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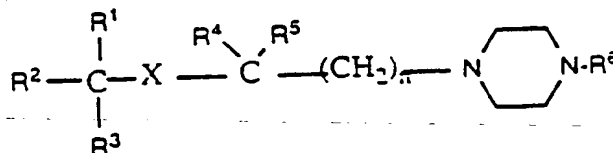
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Tertiary alkyl functionalized piperazine derivatives.

Compounds of the formula



in which R¹ is alkyl; R² and R³ are alkyl or taken together they are polymethylene, R² and R³ complete a 5-norbornen-2-yl moiety; X is -CO₂-, -OCO-, -OCO₂-, -N(R⁷)CO-, -NHNHCO-, -ON(R⁷)CO-, -CON(R⁷)-, -N(R⁷)CO₂-, -OCON(R⁷)- or -N(R⁷)CON(R⁸)-, wherein R⁷ and R⁸ are, independently, hydrogen, alkyl, phenyl, benzyl, substituted phenyl or substituted benzyl in which the substituents are halo, alkyl, alkoxy, cyano, nitro or perhalomethyl; R⁴ is hydrogen or alkyl; R⁵ is hydrogen, alkyl, hydroxyalkyl, phenyl, benzyl, substituted phenyl or substituted benzyl in which the substituents are hydroxy, halo, alkyl, alkoxy, trifluoromethyl, nitro, cyano, carbalkoxy, carboxamido, amino, alkylamino, or dialkylamino; R⁶ is phenyl, benzyl, 2-, 3-, or 4-pyridinyl, 2-pyrimidinyl or 2-pyrazinyl, any of which may be substituted by one or more hydroxy, halo, alkyl, alkoxy, trifluoromethyl, nitro, cyano, carbalkoxy, carboxamido, amino, alkylamino or dialkylamino; n is one of the integers 1, 2, 3, 4 or 5; or a pharmaceutically acceptable salt thereof, with the proviso that when X is -CON(R⁷)- and R⁷ is alkyl, R⁶ is other than 2-pyrimidinyl, are antidepressant and/or anxiolytic agents.

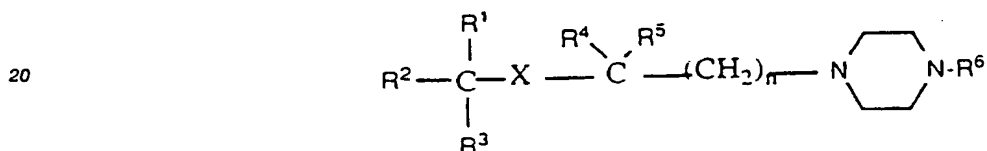
EP 0 395 313 A2

TERTIARY ALKYL FUNCTIONALIZED PIPERAZINE DERIVATIVES

This invention relates to novel tertiary alkyl functional piperazine derivatives, to processes for their preparation, to their use and to pharmaceutical compositions containing them.

The anxiolytic activity of buspirone and structurally related compounds has been attributed to their selective activity at a serotonin (5-hydroxytryptamine; 5-HT) subtype receptor designated the 5-HT_{1A} receptor. U.S. Patent No. 4,202,898 discloses the treatment of anxiety and depression with a group of substituted phenylpiperazine derivatives. Among the compounds disclosed as useful for that purpose is 2,2-dimethylpropanoic acid (3-trifluoromethylthio phenyl-piperazino)ethyl ester (column 3, compound 21). The therapeutic value of 5-HT_{1A} receptor agonists in treating multi-CNS disorders has recently been extended to compound structures such as umespirone which has high affinity for both the 5-HT_{1A} and D₂ receptor binding sites (E.P. DE 3529872, 87/9). US 4,797,489 by Abou-Gharbia et al discloses adamantyl- and fluorenylarylpiperazines and -arylpiperidines which are useful for the treatment of CNS disorders.

In accordance with this invention there is provided a group of novel compounds which exhibit serotonin 5HT_{1A} receptor affinity which characterizes them as antidepressant and/or anxiolytic agents. Some of the compounds of this invention exhibit both 5HT_{1A} receptor affinity and dopamine D₂ receptor binding which characterizes them as anxiolytic and/or antidepressant agents with elements of antipsychotic activity. The compounds of this invention are of the following structural formula:



in which

R¹ is alkyl of 1 to 6 carbon atoms;

R² and R³ are alkyl of 1 to 6 carbon atoms or taken together they are polymethylene of 2 to 12 carbon atoms or taken together with the carbon atom to which they are attached, R² and R³ complete a 5-norbornen-2-yl moiety;

X is -CO₂-, -OCO-, -OCO₂-, -N(R⁷)CO-, -NHNHCO-, -ON(R⁷)CO-, -CON(R⁷)-, -N(R⁷)CO₂-, -OCON(R⁷)- or -N(R⁷)CON(R⁸)-; wherein R⁷ and R⁸ are, independently, hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, benzyl, substituted phenyl or substituted benzyl in which the substituents are halo, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, cyano, nitro or perhalomethyl;

R⁴ is hydrogen or alkyl of 1 to 6 carbon atoms;

R⁵ is hydrogen, alkyl of 1 to 8 carbon atoms, hydroxyalkyl of 1 to 3 carbon atoms, phenyl, benzyl, substituted phenyl or substituted benzyl in which the substituents are hydroxy, halo, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, trifluoromethyl, nitro, cyano, carbalkoxy of 2 to 7 carbon atoms, carboxamido, amino, alkylamino of 1 to 6 carbon atoms or dialkylamino of 2 to 12 carbon atoms;

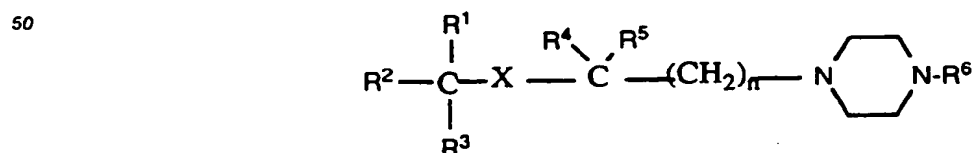
R⁶ is phenyl, benzyl, 2-, 3-, or 4-pyridinyl, 2-pyrimidinyl or 2-pyrazinyl; any of which may be substituted by one or more hydroxy, halo, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, trifluoromethyl, nitro, cyano, carbalkoxy of 2 to 7 carbon atoms, carboxamido, amino, alkylamino of 1 to 6 carbon atoms or dialkylamino of 2 to 12 carbon atoms;

and

n is one of the integers 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt thereof, with the proviso that when X is -CON(R⁷)- and R⁷ is alkyl, R⁶ is other than 2-pyrimidinyl.

The preferred compounds from the standpoint of production economics and activity profile are those of the formula:



R¹ is alkyl of 1 to 6 carbon atoms;

R² and R³ are alkyl of 1 to 6 carbon atoms or taken together they are polymethylene of 2 to 6 carbon atoms or taken together with the carbon atom to which they are attached, R² and R³ complete a 5-norbornen-2-yl moiety;

5 X is -CO₂-, -OCO-, -OCO₂-, -N(R⁷)CO-, -NHNHCO-, -ON(R⁷)CO-, -CON(R⁷)-, -N(R⁷)CO₂-, -OCON(R⁷)- or -N(R⁷)CON(R⁸)-; wherein R⁷ and R⁸ are, independently, hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, benzyl, substituted phenyl or substituted benzyl in which the substituents are halo, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, cyano, nitro or perhalomethyl;

R⁴ is hydrogen or alkyl of 1 to 6 carbon atoms;

10 R⁵ is hydrogen, alkyl of 1 to 6 carbon atoms, hydroxyalkyl of 1 to 3 carbon atoms, phenyl, benzyl, p-hydroxyphenyl, p-methoxyphenyl, o-methoxyphenyl, p-chlorophenyl or p-fluorophenyl;

R⁶ is phenyl, 2-alkylphenyl in which the alkyl substituent has 1 to 6 carbon atoms, 2-alkoxyphenyl in which the alkoxy substituent has 1 to 6 carbon atoms, 2-halophenyl, 2-cyanophenyl, 2-nitrophenyl, 2-perhalomethylphenyl, benzyl, 2-, 3-, or 4-pyridinyl, 2-pyrimidinyl or 2-pyrazinyl;

15 and

n is one of the integers 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt thereof, with the proviso that when X is -CON(R⁷)- and R⁷ is alkyl, R⁶ is other than 2-pyrimidinyl.

20 The halo substituent referred to in the preceding paragraph may be chloro-, bromo-, fluoro- or iodo, the chloro-, bromo- and fluoro- substituents being preferred. For simplicity, the lower alkyl and alkoxy groups containing 1 to 4 carbon atoms are preferred throughout the molecules. The pharmaceutically acceptable salts are produced conventionally from such acids as hydrochloric, hydrobromic, sulfuric, phosphoric, methane sulfonic, nitric, p-toluene sulfonic, acetic, citric, maleic, succinic acid and the like.

25 The compounds of this invention present chiral centers depending upon the substituent variations of R¹, R² and R³ and R⁴ and R⁵. The optical isomers generated at these positions may be separated and isolated or directly produced from reactants of known or related configurations, by conventional means.

30 Highly selective 5HT_{1A} receptor binding has been observed with the compounds of this invention in which R⁵ is alkyl of 4 to 8 carbon atoms or an optionally substituted phenyl or benzyl moiety. These compounds demonstrate only poor relative binding to the D₂ and α₁ receptors. As such, their selective anxiolytic activity is clearly indicated.

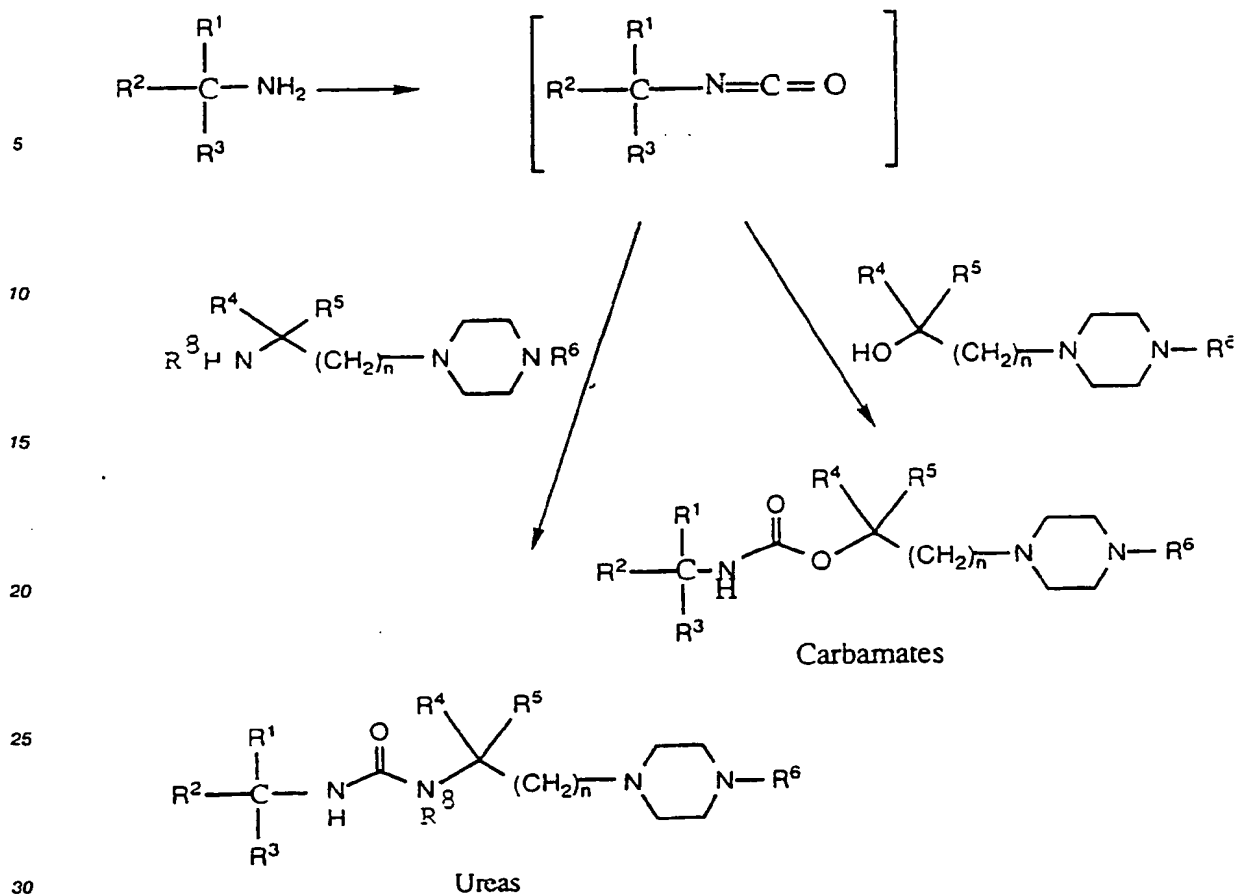
35 The compounds of this invention are produced by various conventional methods from commercially available starting materials or reactants producible by conventional techniques. Thus, for example, the desired tertiary butyl ureas, carbamates, and carbonates can be prepared by reacting tert-alkylamine or tert-alkylalcohol with the appropriate piperazinylalkanol or piperazinylalkylamine in the presence of phosgene or an appropriate phosgene equivalent such as trichloromethyl chloroformate in a suitable solvent such as methylene chloride, e.g.

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Reaction of the above piperazinyllalkylamine with a compound of formula



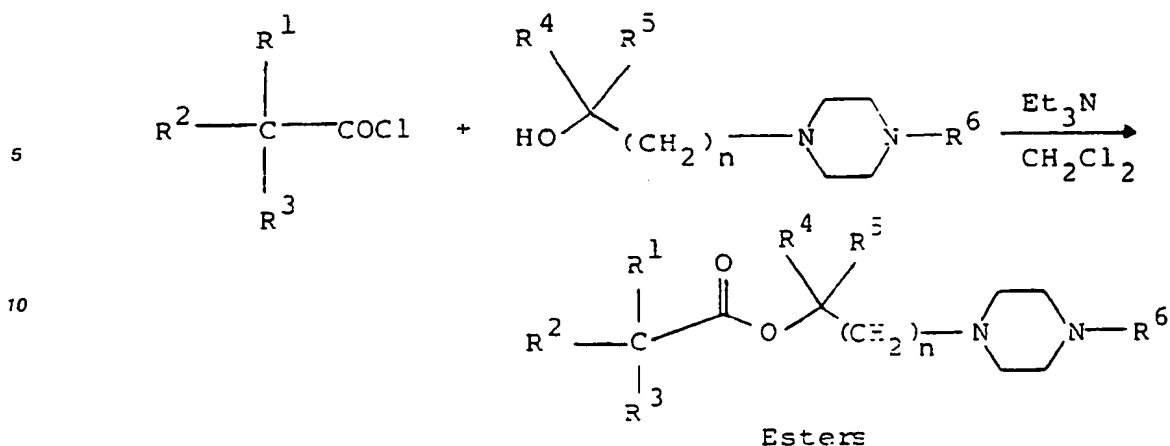
40 (where Hal is halogen) gives a carbonate.

The desired esters may be prepared by esterification of the appropriately substituted piperazinyllalkanol, eg with an acid halide in a suitable solvent such as CH_2Cl_2 in the presence of an acid acceptor such as triethylamine.

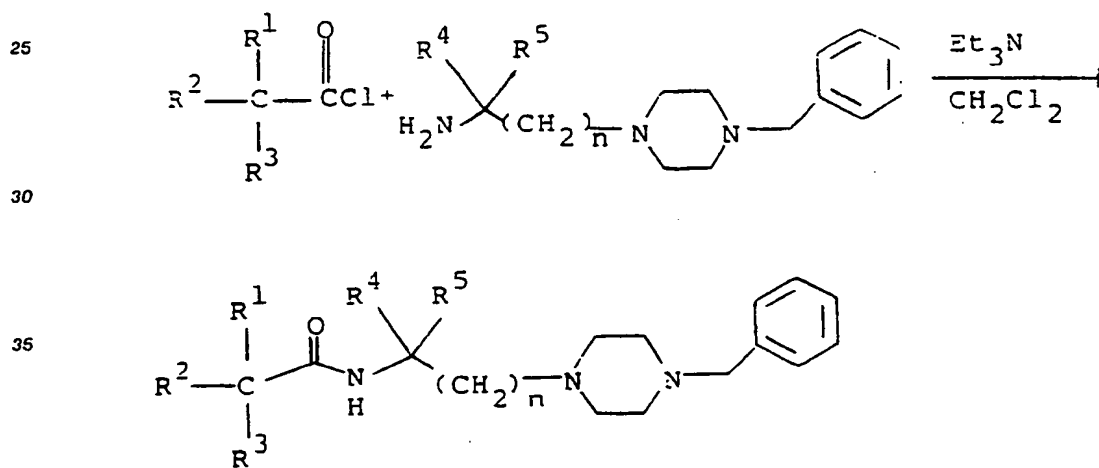
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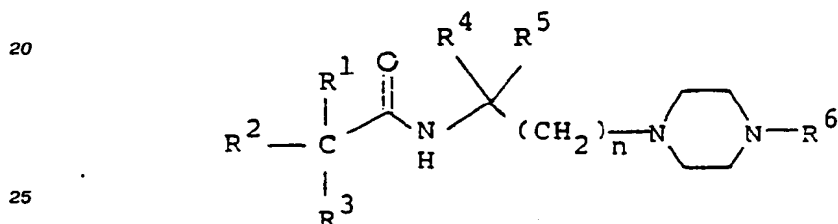
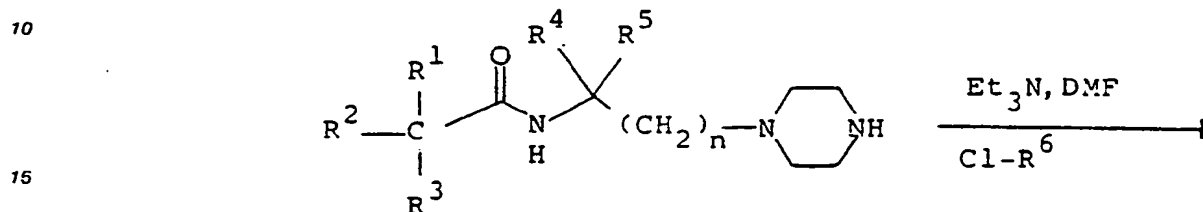
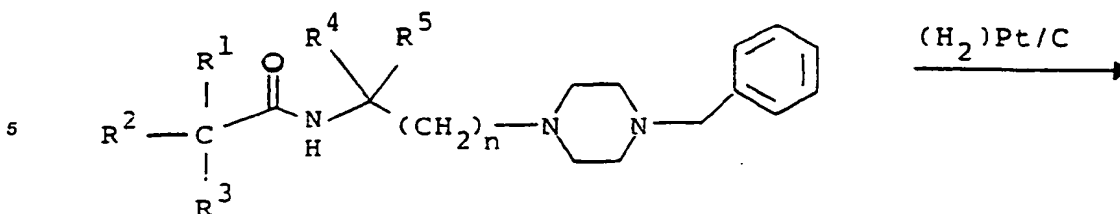
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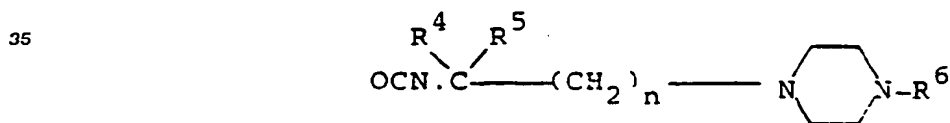
20 The desired α -substituted carboxamides can be prepared by acylating a corresponding amine. In one example the appropriately substituted N-benzylpiperazinyalkylamine is acylated by reaction with an acid halide in methylene chloride and in the presence of triethylamine to afford the N-benzylcarboxamide intermediate, which is debenzylated to give an intermediate compound in which R^6 is hydrogen. This may be alkylated to the compound of the invention, eg by reaction with the appropriate aryl- or heteroarylhalide. An example of the process is illustrated below:





Carboxamides

30 Of course, the reverse esters, amides and carbamates are prepared in the same manner with the oppositely functional reactants. Thus the reverse carbonate may be prepared by reacting a piperazine isocyanate of formula

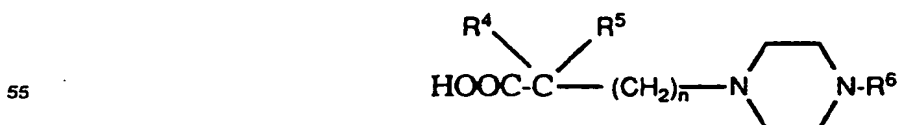


40 with an alcohol of formula.

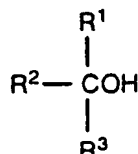
In one method for preparing the reverse amide (in which X is $\text{NR}^7\text{CO}-$) an amine of the formula:



50 is acylated with an acid of the formula:

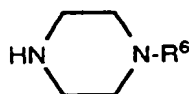


or with any acylating derivative thereof. Examples of acylating derivatives include the acid halides (eg. acid chlorides), azides, anhydrides, imidazolides (eg obtained from carbonyldiimidazole), activated esters or O-acyl ureas obtained from a carbodiimide such as a dialkylcarbodiimide particularly dicyclohexylcarbodiimide. Preferably the amine is acylated with the acid in presence of a coupling agent such as 1,1'-carbonyldiimidazole, iso-butylchloroformate or diphenylphosphinyl chloride. The hydrazides and hydroxamates are produced in the same manner from the substituted hydrazine or substituted hydroxylamine and the desired carboxylic acid. A reverse ester of the invention (ie a compound where X is -OCO-) may be prepared by esterification of the above acid with an alcohol of the formula:

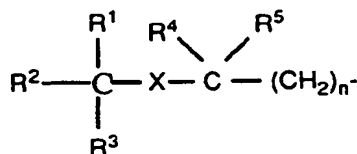


Esterification may be carried out by the general methods known in the art.

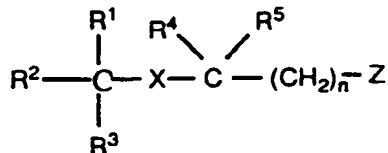
An alternative method of preparing the compounds of the invention comprises alkylation of a piperazine of the formula:



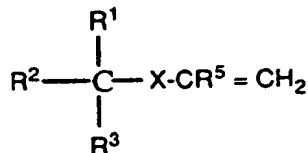
with an alkylating agent providing the group:



The alkylating agent may be, for example, a compound of the formula:

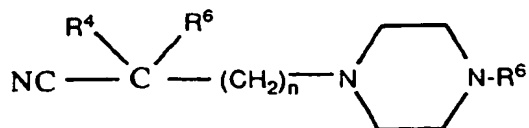


where Z is a leaving group such as halogen or an alkyl- or aryl-sulphonyloxy group. Alternatively where n is 1 the alkylating agent may be an unsaturated compound of the formula:

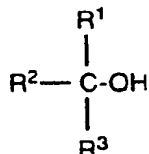


and the compounds are reacted by means of a Michael reaction. The reaction may be carried out at elevated temperature in the presence of an alcohol.

The amides of the invention in which X is -NH-CO- may be prepared by an alternative method comprising reacting a nitrile of the formula:

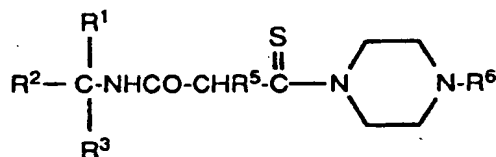


with the tertiary alcohol of the formula:

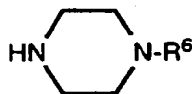


under acidic conditions as in the Ritter reaction.

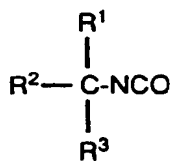
A further method of preparing the reverse amides of the invention in which n is 1 comprises the desulphurisation of a sulphur containing compound of the formula:



The desulphurisation may be carried out in the presence of a nickel catalyst. The sulphur containing compound may be prepared by a Willgerodt reaction, eg. an aryl alkyl ketone of the formula $\text{CH}_3\text{CO-R}^5$ is reacted with sulphur and a piperazine of the formula:



and the resulting thioamide is treated with a base and with an isocyanate of the formula:



The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

The following Examples illustrate, without limitation, the preparation of representation compounds of this invention.

Example 1

N-(1,1-Dimethylethyl)-N'-[4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl]urea

To a suspension of tert-butylamine (0.4 g, 0.005 mol) in 50 mL of dry methylene chloride under a dry nitrogen atmosphere was added triethylamine (1.2 g, 0.01 mol). The resulting solution was refluxed for thirty minutes, and then trichloromethyl chloroformate (0.57 g, 0.002 mol) was added dropwise via syringe and the resulting suspension was refluxed for three hours. The reaction mixture was then allowed to cool to room temperature, and to the cold solution was added a solution of 2-[4-(2-methoxyphenyl)-1-piperazinyl]-butylamine (1.5 g, 0.005 mol) in 15 mL of dry methylene chloride, followed by an additional two equivalents of triethylamine (1.2 g, 0.01 mol). The resulting mixture was allowed to stir at room temperature overnight. The reaction mixture was diluted to 200 mL with methylene chloride, washed with 5% aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator to a yellow oil. The desired product (TLC on silica gel using a 20% methanol in ethyl acetate solvent mixture, $R_f = 0.41$) was isolated by gravity chromatography on silica gel and converted to the hydrochloride salt to afford 0.33 g of the title compound as a trihydrochloride, mp. = 167-169°C.

Elemental analysis for $C_{20}H_{34}N_4O_2 \cdot 3HCl$			
Calc'd:	C, 50.90;	H, 7.90;	N, 11.87
Found:	C, 51.04;	H, 8.04;	N, 11.75

Example 2**N-[4-[4-(2-Methoxyphenyl)-1-piperazinyl] butyl]-2,2-dimethylpropanamide**

To a stirred solution of 4-(2-methoxyphenyl)-1-piperazinylbutanamine (1.71 g, 0.006 mol) and triethylamine (0.8 g, 0.008 mol) in 50 mL of methylene chloride, pivaloyl chloride (0.78 g, 0.006 mol) was added and stirring was continued overnight at room temperature. The methylene chloride solution was washed with water, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The desired product was isolated by high pressure liquid chromatography (HPLC) on silica gel (using a gradient consisting of from 10% ethyl acetate in hexane to 10% methanol in ethyl acetate) and converted to the dihydrochloride salt (0.95 g, 38%), mp. = 191-196°C.

Elemental analysis for $C_{20}H_{33}N_3O_2 \cdot 2HCl \cdot 1/2 H_2O$			
Calc'd:	C, 55.94;	H, 8.22;	N, 9.79
Found:	C, 56.03;	H, 8.24;	N, 9.89

Example 3**2,2-Dimethylpropanoic acid 2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl ester**

Pivaloyl chloride (15.0 g, 0.124 mol) and triethylamine (13.1 g, 0.13 mol) were stirred with 1-bromoethanol (15.5 g, 0.124 mol) in CH_2Cl_2 at room temperature. The desired product, 2-bromoethyl-

pivalate was recovered for use in the following procedure.

To a stirred solution of N-(2-methoxyphenyl)piperazine (3.64 g, 0.019 mol) and triethylamine (6 g, 0.06 mol) in 80 mL of DMF was added 2-bromoethylpivalate (4 g, 0.019 mol). The reaction mixture was stirred overnight at room temperature. The DMF was removed under reduced pressure and the residue was dissolved in 100 mL of methylene chloride. The organic layer was washed with water, dried (anhydrous Na₂SO₄) and evaporated. The desired product was separated by preparative HPLC and converted to the dihydrochloride salt, mp. = 193-195 °C.

Elemental analysis for C ₁₈ H ₂₈ N ₂ O ₃ · 2HCl				
Calc'd:	C, 54.96;	H, 7.63;	N, 7.12;	Cl, 18.07
Found:	C, 54.94;	H, 7.52;	N, 6.97;	Cl, 17.69

Calc'd:	C, 54.96;	H, 7.63;	N, 7.12;	Cl, 18.07
Found:	C, 54.94;	H, 7.52;	N, 6.97;	Cl, 17.69

Example 4

2,2-Dimethylpropanoic acid 3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl ester

To a stirred solution of 3-[4-(2-methoxyphenyl)-1-piperazinyl]propanol (4.76 g, 0.019 mol) and triethylamine (6 g, 0.06 mol) in 100 mL of methylene chloride was added pivaloyl chloride (2.28 g, 0.019 mol) and stirring was continued overnight at room temperature. The organic layer was washed with water, dried (anhydrous Na₂SO₄) and evaporated. The title compound was isolated by preparative HPLC and converted to the dihydrochloride salt; mp. = 202-204 °C.

Elemental analysis for C ₁₉ H ₃₀ N ₂ O ₃ · 2HCl			
Calc'd:	C, 56.01;	H, 7.86;	N, 6.87
Found:	C, 56.13;	H, 8.09;	N, 6.73

Calc'd:	C, 56.01;	H, 7.86;	N, 6.87
Found:	C, 56.13;	H, 8.09;	N, 6.73

Example 5

2,2-Dimethylpropanoic acid 3-[4-(2-chlorophenyl)-1-piperazinyl]propyl ester

The title compound was prepared following procedure of Example 4 with the exception that 3-[4-(2-chlorophenyl)-piperazine]propanol (4.89 g, 0.019 mol) was used instead of 3-[4-(2-methoxyphenyl)-piperazinyl]propanol. The title compound was converted to the hydrochloride salt, mp. = 186-188 °C.

Elemental analysis for C ₁₈ H ₂₇ N ₂ O ₂ · HCl			
Calc'd:	C, 57.06;	H, 7.46;	N, 7.46
Found:	C, 57.73;	H, 7.06;	N, 7.13

Calc'd:	C, 57.06;	H, 7.46;	N, 7.46
Found:	C, 57.73;	H, 7.06;	N, 7.13

Example 6

2,2-Dimethylpropanoic acid 3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl ester

Pivaloyl chloride (15.0 g, 0.124 mol) and triethylamine (13.1 g, 0.13 mol) were stirred with 1-bromopropanol (17.3 g, 0.124 mol) in CH_2Cl_2 at room temperature. The desired product, 3-bromopropyl-pivalate was recovered for use in the following procedure.

To a stirred solution of N-(2-pyrimidinyl)piperazine dihydrochloride (4.25 g, 0.0179 mol) and triethylamine (6.06 g, 0.06 mol) in DMF was added 3-bromopropyl pivalate (4.0 g, 0.0179 mol) and the solution was stirred overnight at room temperature. The solvent was evaporated and the residue dissolved in CH_2Cl_2 . The CH_2Cl_2 extract was washed with water, dried (anhydrous Na_2SO_4) and evaporated to afford 9.0 g of crude title compound. Purification by HPLC and conversion to the dihydrochloride with ethereal HCl yielded the product, mp. 178-180 °C.

Elemental analysis for $\text{C}_{16}\text{H}_{26}\text{N}_4\text{O}_2 \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$			
Calc'd:	C, 48.36;	H, 7.55;	N, 14.10
Found:	C, 48.00;	H, 7.08;	N, 13.70

Example 7

(R)-N-[1-Methyl-2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl] trimethylacetamide

To a chilled solution of t-butoxycarbonyl D-alanine (9.45 g, 0.05 mol) and 1-(2-methoxyphenyl)-piperazine (9.6 g, 0.05 mol) in 125 mL of CH_2Cl_2 was added diethyl cyanophosphonate (8.34 mL, 0.055 mol) in 50 mL of CH_2Cl_2 over 30 minutes followed by triethylamine (7.37 mL, 0.055 mol) in 50 mL of CH_2Cl_2 over 15 minutes. After 2.5 hour, the solution was washed with water (2 x 100 mL) and K_2CO_3 (2 x 100 mL of 10% aqueous), dried over anhydrous K_2CO_3 and evaporated to an oil. The crude 1-(t-butoxycarbonyl-D-alanyl)-4-(2-methoxyphenyl)piperazine was stirred in 200 mL of 4.5 N HCL in ethyl acetate for 1 hour at room temperature, diluted with 400 mL of anhydrous diethyl ether, filtered, washed and dried in vacuo. The 1-(D-alanyl)-4-(2-methoxyphenyl)piperazine dihydrochloride was stirred in 200 mL of anhydrous THF, treated with 225 mL of 1M BH_3 in THF, and refluxed 3.5 hours. After cooling in ice, the reaction was quenched with 140 mL of 2N aqueous HCl and refluxed 18 hours. THF was removed on a Rotovapor®, the aqueous solution was made basic with 6N sodium hydroxide and the amine was extracted into diethyl ether. The ether solution was dried over anhydrous K_2CO_3 , filtered and acidified with 4.5 N HCl in ethyl acetate. The salt was filtered, washed with diethyl ether, converted to the free base in 2 N NaOH and extracted into diethyl ether. After drying as above and evaporation, the (R)-1-methyl-2-[4-(2-methoxyphenyl)piperazinyl]-ethylamine was obtained as an oil (11.8 g, 94.7% based on Boc-D-alanine). A sample was converted to the trihydrochloride sesquihydrate, mp. 219-221 °C; $[\alpha]_{\text{D}}^{25} = -26.4^\circ \text{C} = 0.99 \text{ MeOH}$. ^1H NMR ($\text{DMSO}-d_6$) δ : 1.32 (d, 3H), 3.8 (s, 3H), 6.9-7.0 (m, 4H), IR was devoid of carbonyl peaks.

Elemental analysis for $\text{C}_{14}\text{H}_{23}\text{N}_3\text{O} \cdot 3\text{HCl} \cdot 1.5 \text{H}_2\text{O}$			
Calc'd:	C, 43.59;	H, 7.58;	N, 10.89
Found:	C, 43.47;	H, 7.08;	N, 10.57

(R)-[1-methyl-2-[4-(2-methoxyphenyl)-1-piperazinyl]ethylamine (2.49 g, 0.01 mol) and trimethylacetic acid (2.04 g, 0.02 mol) in 25 mL of CH₂Cl₂ were chilled in ice and treated with diethylcyanophosphonate (3.26 g, 3.1 mL, 0.02 mol) in 10 mL of CH₂Cl₂ over 15 minutes followed by N-methylmorpholine (2.02 g, 2.2 mL, 0.02 mol) in 10 mL CH₂Cl₂ over 15 minutes and the reaction was followed by TLC. The reaction was essentially complete after 2 hours. After stirring overnight, the solution was washed with 2N NaOH (2 x 50 mL), and water (2 x 50 mL) and dried (anhydrous K₂CO₃). The product was isolated using dry column chromatography on silica gel (300 g) and development with ethyl acetate. The fraction containing the product (R_f 0.54, uniplate, ethyl acetate) was evaporated to give 3.35 g (98% yield) as an oil which was dissolved in 150 mL anhydrous diethyl ether and precipitated with 4.5 N HCl in ethyl acetate, mp. 185-188 °C. Recrystallization of a small sample from methanol and diethyl ether did not change the melting point. IR 1650 cm⁻¹. ¹H NMR (DMSO d₆) δ: 1.1 (d, 12H), 3.7 (s, 3H), 7.0 (m, 4H), [α]_D²⁵ = -11.67, c 1.03 MeOH

Elemental analysis C ₁₉ H ₃₁ N ₃ O ₂ · 2HCl				
Calc'd:	C, 56.15;	H, 8.18;	N, 10.34;	Cl, 17.45
Found:	C, 55.76;	H, 7.98;	N, 9.98;	Cl, 17.16;

Calc'd:	C, 56.15;	H, 8.18;	N, 10.34;	Cl, 17.45
Found:	C, 55.76;	H, 7.98;	N, 9.98;	Cl, 17.16;

Example 8**N-2-(4-(2-Methoxyphenyl)-1-piperazine)ethyl 2,2-dimethylpropanamide**

To a solution of 2-(4-(2-methoxyphenyl)-1-piperazine)ethyl amine (3.00 g, 0.0127 mol) in CH₂Cl₂ (80 mL) were added trimethylacetyl chloride (1.6 mL, 1.6 g, 0.013 mol) and triethylamine (2.0 mL, 2.8 g, 0.027 mol) successively. The solution was stirred at room temperature for 24 hours. The solution was washed with H₂O and then brine and was dried with MgSO₄ and upon evaporation of CH₂Cl₂ gave 4.25 g of crude product. Purification by flash chromatography (silica gel, hexane, EtOAc, MeOH) provided a pure sample of the free base, 1.19 g. An additional 2.29 g of slightly impure product was recovered. Treatment of the pure sample in EtOH with HCl gave the dihydrochloride of the title compound, 1.13 g, mp. 243-244 °C.

Elemental analysis for C ₁₈ H ₂₉ N ₃ O ₂ · 2HCl			
Calc'd:	C, 55.10;	H, 7.96;	N, 10.71
Found:	C, 54.78;	H, 8.05;	N, 10.56

Calc'd:	C, 55.10;	H, 7.96;	N, 10.71
Found:	C, 54.78;	H, 8.05;	N, 10.56

Example 9**N-(1,1-Dimethylethyl)-4-(2-methoxyphenyl)-1-piperazineacetamide**

To a solution of t-butyl chloroacetamide (3.51 g, 0.0235 mol) in DMF (150-200 mL) was added successively 1-(2-methoxyphenyl)piperazine hydrochloride (5.35 g, 0.0234 mol) and triethyl amine (6.85 mL, 4.97 g, 0.0491 mol). The solution was stirred at 90 °C for 4 hours. The DMF was evaporated under reduced pressure. The residue was partitioned between CH₂Cl₂ and H₂O. The aqueous phase was extracted once with CH₂Cl₂. The combined organic phases were washed once with a small amount of H₂O and dried with MgSO₄. Evaporation of the solvent gave the crude product (6.24 g) which was purified by flash chromatog-

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raphy (silica gel, EtOAc, hexane) to yield the free base (4.8 g). Treatment with HCl in EtOH gave the title compound as the dihydrochloride, mp. 105 ° C (3.97 g, 43%).

Elemental analysis for $C_{17}H_{27}N_3O_2 \cdot 2HCl \cdot H_2O$			
Calc'd:	C, 51.51;	H, 7.88;	N, 10.670
Found:	C, 51.59;	H, 8.16;	N, 10.39

Example 10

N-(1,1-Dimethylethyl)-4-(2-pyrimidinyl)-1-piperazinepropanamide

To a suspension of t-butylamine hydrochloride (prepared by treatment of an Et₂O solution of t-butylamine (2.7 mL, 1.9 g, 0.026 mol) with HCl) in a solution of 3-bromopropionic acid chloride (4.47 g, 0.0261 mol) with CH₂Cl₂ (145 mL) was added N,N-diisopropylethylamine (9.1 mL, 6.8 g, 0.052 mol) over 10-15 minutes at room temperature. The solution was stirred at room temperature for 2.5-3 hours. A few mL's of N,N-diisopropylethylamine were added until the solution became homogeneous. The solution was washed twice with dilute HCl and once with H₂O, dried with MgSO₄ and evaporated to provide 3.34 g of N-tert-butyl 3-bromopropanamide and N-tert-butyl acrylamide (approximately 36%/64% by weight). The reaction mixture was taken up in EtOH (200 mL), and to the solution of amides was added 1-(2-pyrimidinyl)-piperazine dihydrochloride (6.82 g, 0.0288 mol) and sodium acetate (4.72 g, 0.0575 mol). The mixture was refluxed for 8 days. The solvent was evaporated. The residue was partitioned between CH₂Cl₂ and aqueous Na₂CO₃. The CH₂Cl₂ phase was washed with aqueous NaCl and dried with MgSO₄. Evaporation of the CH₂Cl₂ gave 5.61 of crude compound which was purified by HPLC to give 4.13 g of free base. Treatment in EtOH with HCl gave the title compound, 4.48 g (46%), mp 220-222 ° C.

Elemental analysis for $C_{15}H_{25}N_5O \cdot 2HCl$ 1/2 H ₂ O			
Calc'd:	C, 48.25;	H, 7.55;	N, 18.76
Found:	C, 48.42;	H, 7.45;	N, 18.62

Example 11

2,2-Dimethylpropanoic acid 2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl ester

Following the procedure of Example 3, with the exception that N-(2-pyrimidinyl)piperazine was substituted for N-(2-methoxyphenyl)piperazine, afforded the title compound which was converted to the dihydrochloride salt with ethereal HCl, mp. 185-187 ° C.

Elemental analysis for $C_{15}H_{24}N_4O_2 \cdot 2HCl$			
Calc'd:	C, 49.32;	H, 7.12;	N, 15.34
Found:	C, 38.24;	H, 3.69;	N, 37.87

5

Example 12

10

Tertiary-butyl 3-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylpropanoate

15

A stirred suspension of 2-chloro-1-methylpyridinium iodide (3.28 g, 12.8 mmol) in toluene (20 mL) was treated under an atmosphere of nitrogen with atropic acid (1.80 g, 12.2 mol) treated with tert-butanol (0.92 mL, 11.8 mmol), treated with triethylamine (3.6 mL, 25.8 mmol), heated under reflux for 2 hours, cooled to room temperature and treated with water (100 mL) and diethyl ether (100 mL). The layers were separated and the aqueous layer extracted with diethyl ether (50 mL). The organic phases were combined, washed with water (100 mL), dried ($MgSO_4$), evaporated in vacuo, and the residue purified by chromatography [silica; hexane-ethyl acetate (20:1)] to give tert-butyl 2-phenylpropenoate (1.32 g) as an oil.

20

A solution of tert-butyl 2-phenylpropenoate (1.28 g, 6.3 mmol) and 1-(2-methoxyphenyl)piperazine (1.22 g; 6.4 mmol) in ethanol (10 mL) was maintained at room temperature for 3 days, evaporated in vacuo, and the yellow oil purified by chromatography [silica; hexane-ethyl acetate (5:1)] to give the free base of the product (1.96 g) as colorless crystals, mp. 99-101 °C.

25

A suspension of free base in hot methanol (20 mL) was acidified with ethereal hydrogen chloride. The resulting solution was cooled to cool temperature and the mixture evaporated in vacuo. The crystals were triturated with diethyl ether to give the dihydrochloride salt of the product (1.56 g), mp. 190-193 °C.

30

Elemental analysis for $C_{24}H_{32}N_2O_3 \cdot 2HCl$			
Calc'd:	C, 61.4;	H, 7.3;	N, 6.0
Found:	C, 61.3;	H, 7.5;	N, 6.0

35

40

Example 13

45

N-Tertiary-butyl 3-[4-(2-methoxyphenyl)piperazinyl]-2-phenylpropanamide

1-(2-Methoxyphenyl)piperazine (22.6 g, 0.118 mol) and atropic acid (17.4 g, 0.118 mol) in ethanol (300 mL) were heated under reflux for 18 hours, cooled to room temperature, and evaporated in vacuo. The solid was triturated with acetone (3 x 100 mL) to give a first crop of 3-[4-(2-methoxyphenyl)piperazinyl]-2-phenylpropionic acid (13.8 g) as white crystals. The filtrate was evaporated in vacuo to give an oil which slowly crystallized over 1 month. The solid was triturated with acetone (200 mL) to give a second crop of the same hemihydrate product (9.01 g) as white crystals, mp. 160-163 °C.

50

55

Elemental analysis for $C_{20}H_{24}N_2O_3 \cdot 1/2 H_2O$			
Calc'd:	C, 68.8;	H, 7.2;	N, 8.0
Found:	C, 68.4;	H, 7.2;	N, 7.9

5

10 A stirred suspension of 3-[4-(2-methoxyphenyl)piperazinyl]-2-phenylpropionic acid (5.05 g; 14.7 mmol) in dichloromethane (30 ml) was treated with 1,1-carbonyldiimidazole (2.67 g, 16.5 mmol) and, after 35 minutes, the resulting solution was treated with tert-butylamine (1.9 ml, 18.2 mmol). After 18 hours, the mixture was evaporated in vacuo and the residue purified by chromatography (silica, diethyl ether) to give the product (2.80 g, 48%) as white crystals. A suspension of the solid in methanol-isopropanol (2 ml + 6 ml) was acidified with ethereal hydrogen chloride to give a solution which was evaporated in vacuo to give a solid. Trituration with diethyl ether gave the dihydrochloride salt of the product (3.30 g), mp. 230-231 °C.

15

Elemental analysis for $C_{24}H_{33}N_3O_2 \cdot 2HCl$			
Calc'd:	C, 61.5;	H, 7.5;	N, 9.0
Found:	C, 61.4;	H, 7.5;	N, 8.9

20

25

Example 14**30 N-Tertiary-butyl 2-[[4-(2-methoxyphenyl)piperazinyl]methyl]-3-phenyl-propanamide**

35 2-(Phenylmethyl)propenoic acid (Mannich et al., Chem. Ber., 1922, 55, 3486) (2.00 g, 12.35 mmol) and 1-(2-methoxyphenyl)piperazine (2.37 g, 12.35 mmol) in propanol (25 mL) were boiled under reflux for 18 hours, cooled to room temperature, and evaporated in vacuo. The residue was triturated with acetone and diethyl ether to give 2-[[4-(2-methoxyphenyl)piperazinyl]methyl]-3-phenyl propanoic acid (0.80 g) as a colorless powder, mp. 155-158 °C.

40

Elemental analysis for $C_{21}H_{26}N_2O_3$			
Calc'd:	C, 71.2;	H, 7.3;	N, 7.9
Found:	C, 71.6;	H, 7.4;	N, 7.6

45

45 The product of the preceding paragraph (1.60 g, 4.5 mmol) in dichloromethane was treated with 1,1'-carbonyldiimidazole (0.73 g, 4.5 mmol), stirred for one hour, treated with tertiary butylamine (0.66 g, 9.0 mmol), stirred for eighteen hours, evaporated in vacuo and the residue was chromatographically purified (silica; diisopropyl ether gradient to diethyl ether). The product was dissolved in hot isopropanol and treated with ethereal HCl to obtain the title compound as the hydrochloride salt (0.43 g), mp. 127.5-130 °C.

50

Elemental analysis for $C_{25}H_{35}N_3O_2 \cdot HCl \cdot 3/4 H_2O$			
Calc'd:	C, 65.4;	H, 8.2;	N, 9.2
Found:	C, 65.1;	H, 8.0;	N, 8.9

55

Example 15**N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-1-methylcyclohexanecarboxamide**

To a solution of 2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl amine (1.49 g, 0.00633 mol) in CH₂Cl₂ (40 mL), 1-methylcyclohexylcarboxylic acid chloride (1.00 g, 0.00622 mol) and triethylamine (1.0 mL, 0.73 g, 0.0072 mol) were added and the mixture stirred at room temperature overnight. The solution was washed with water and dried with MgSO₄. Evaporation gave 2.28 g of crude material which was purified by HPLC to give the pure free base, 1.54 g. Treatment with HCl in EtOH gave the title compound as the dihydrochloride, 1.36 g (51%), mp. 180-197°C.

Elemental analysis for C₂₁H₃₃N₃O₂ • 2
HCl • 1/2 H₂O

Calc'd:	C, 57.13;	H, 8.22;	N, 9.52
Found:	C, 57.40;	H, 7.93;	N, 9.39

Example 16**4-(2-Methoxyphenyl)-N-(1-methylcyclohexyl)-1-piperazinepropanamide**

To a suspension of 1-methyl-cyclohexylamine hydrochloride (4.59 g, 0.0307 mol) in CH₂Cl₂ (150 mL) was added 3-bromopropionyl chloride (5.26 g, 0.0307 mol). Diisopropyl ethyl amine (20.7 mL, 15.4 g, 0.119 mol) was added slowly. The mixture was stirred at room temperature overnight. The organic phase was filtered, washed and aqueous HCl, water, and dried with MgSO₄. Evaporation of the CH₂Cl₂ gave 5.03 g of a mixture of N-1-methylcyclohexyl-2-bromo propanamide and N-1-methylcyclohexyl acrylamide in a ratio of 1 to 3. This mixture (3.0 g, 0.016 mol) was taken up in EtOH (142 mL). To this solution was added 1-(2-methoxyphenyl)piperazine hydrochloride (4.34 g, 0.0190 mol) and sodium acetate (1.58 g, 0.0193 mol). The mixture was refluxed two days. The EtOH was evaporated. The residue was partitioned between H₂O and CH₂Cl₂. The CH₂Cl₂ phase dried with MgSO₄. Evaporation of CH₂Cl₂ gave crude product, 6.77 g. Purification by HPLC gave the pure free base, 2.38 g, which was treated with HCl in EtOH to give the title compound as the dihydrochloride, 2.53 g (37%, based on the amide mixture), mp. 198-203°C.

Elemental analysis for C₂₁H₃₃N₃O₂ • 2HCl

Calc'd:	C, 58.33;	H, 8.16;	N, 9.72
Found:	C, 58.00;	H, 8.39,	N, 9.63

Exempl 17**4-(2-Pyrimidinyl)-N-(1-methylcyclohexyl)-1-piperazinepropanamide**

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The title compound was prepared from -1-(2-pyrimidyl)piperazine dihydrochloride (2.77 g, 0.0117 mol), sodium acetate (1.92 g, 0.0234 mol) and the mixture of 3-N-1-methylcyclohexyl-bromopropanamide and N-1-methylcyclohexyl acrylamide (1.8 g, 0.0098 mol) in the manner described in Example 16 to give 1.36 g of the title compound as the dihydrochloride (32%, based on the amide mixture), mp. 204-209°C.

Elemental analysis for $C_{18}H_{29}N_5O \cdot 2 HCl$ $\cdot 3/2 H_2O$			
Calc'd:	C, 50.1;	H, 7.94;	N, 16.24
Found:	C, 49.84;	H, 7.97;	N, 16.19

Example 18

N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-N'-(1-methylcyclohexyl)urea

To a solution of oxalyl chloride (35 mL, 51 g, 0.40 mol) in CH_2Cl_2 (214 mL) at room temperature was added solid 1-methyl-1-cyclohexanecarboxylic acid (20.05 g, .1410 mol). The solution was stirred at room temperature overnight. The solvent and excess oxalyl chloride were evaporated. The residue was stripped with CH_2Cl_2 twice. The 1-methyl-1-cyclohexanecarboxylic acid chloride (20.00 g, 0.1425 mol) in Et_2O , (110 mL) was added to a stirred suspension of concentrated aqueous NH_3 (31 mL) in Et_2O 300 mL at room temperature. The mixture was stirred at room temperature for 3-4 hours. The aqueous layer was acidified to pH 1-2 with 6 M HCl and brine was added. The Et_2O layer was separated and washed once with aqueous NaCl, dried with $MgSO_4$ and evaporated to remove the Et_2O to give 16.40 g of the desired carboxamide. To a solution of Br_2 (3.7 mL, 11 g, 0.072 mol) in 20% KOH in H_2O (197 mL) at 0°C was added solid 1-methyl-1-cyclohexanecarboxamide (10.00 g, 0.07082 mol). The solution was stirred for 2-3 hours at 0°C and then extracted with Et_2O twice. Drying with $MgSO_4$ and evaporation of the Et_2O gave 1-methyl-1-cyclohexylisocyanate (5.84 g) as an oil which crystallized slowly.

To a solution of 2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl amine (2.02 g, 0.00858 mol) in CH_2Cl_2 (50 mL) was added 1-methylcyclohexyl isocyanate (1.20 g, 0.00862 mol) and the mixture was stirred at room temperature overnight. The mixture was washed once with H_2O , dried with $MgSO_4$ and evaporated to give the crude product (3.53 g) which was purified by HPLC to give the free base, (2.04 g). Treatment with HCl in EtOH gave the title compound as the dihydrochloride (1.06 g, 26%), mp. 155-161°C.

Elemental analysis for $C_{21}H_{34}N_4O_2 \cdot 2HCl$ $\cdot 3/2 H_2O$			
Calc'd:	C, 53.16;	H, 8.29;	N, 11.81
Found:	C, 53.26;	H, 8.24;	N, 11.75

Example 19

N-2-(4-(2-Pyrimidinyl)-1-piperazinyl)ethyl-1-methylcyclohexylcarboxamide

The title compound was prepared from 2-(4-(2-pyrimidinyl)-1-piperazinyl)ethyl amine (1.50 g, 0.00724 mol), 1-methylcyclohexylcarboxylic acid chloride (1.16 g, 0.00722 mol) and triethylamine (1.1 mL, 0.80 g.

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0.0079 mol) in the manner previously described to give 1.80 g (62%) of product, mp. 212-220°C.

Elemental analysis for $C_{18}H_{29}N_5O \cdot 2 HCl$			
Calc'd:	C, 53.47;	H, 7.73;	N, 17.32
Found:	C, 53.1;	H, 7.77;	N, 17.15

Example 20

(R)-N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]-1-methylethyl]-1-methylcyclohexane carboxamide

To a chilled solution of t-butoxycarbonyl D-alanine (9.45 g, 0.05 mol) and 1-(2-methoxyphenyl)-piperazine (9.6 g, 0.05 mol) in 125 mL of CH_2Cl_2 was added diethyl cyanophosphonate (8.34 mL, 0.055 mol) in 50 mL of CH_2Cl_2 over 30 minutes followed by triethylamine (7.37 mL, 0.055 mol) in 50 mL of CH_2Cl_2 over 15 minutes. After 2 1/2 hours, the solution was washed with water (2 x 100 mL) and K_2CO_3 (2 x 100 mL of 10% aqueous), dried over anhydrous K_2CO_3 and evaporated to an oil. The crude 1-(t-butoxycarbonyl-D-alanyl)-4-(2-methoxyphenyl)piperazine was stirred in 200 mL of 4.5 N HCl in ethyl acetate for 1 hour at room temperature, diluted with 400 mL of anhydrous diethyl ether, filtered, washed and dried in vacuo. The 1-(D-alanyl)-4-(2-methoxyphenyl)piperazine dihydrochloride was stirred in 200 mL of anhydrous tetrahydrofuran, treated with 225 mL of 1M BH_3 in tetrahydrofuran, and refluxed 3 1/2 hours. After cooling in ice, the reaction was quenched with 140 mL of 2N aqueous HCl and refluxed 18 hours. The tetrahydrofuran was removed on a Rotovapor, the aqueous solution was made basic with 6N sodium hydroxide and the amine was extracted into diethyl ether. The diethyl ether solution was dried over anhydrous K_2CO_3 , filtered and acidified with 4.5 N HCl in ethyl acetate. The salt was filtered, washed with diethyl ether, converted to free base in 2 N NaOH and extracted into diethyl ether. After drying as above and evaporation, (R)-1-methyl-2-[4-(2-methoxyphenyl)-piperazinyl]ethylamine was obtained as an oil (11.8 g, 94.7% based on BOC-D-alanine). A sample was converted to the trihydrochloride sesquihydrate, mp. 219-221°C; $[\alpha]_D^{25} = -26.4^\circ c = 0.99$ MeOH. 1H NMR ($DMSO-d_6$) δ : 1.32 (d, 3H), 3.8 (s, 3H), 6.9-7.0 (m, 4H). The IR curve was devoid of carbonyl peaks.

Elemental analysis for $C_{14}H_{23}N_3O \cdot 3HCl \cdot 1.5 H_2O$			
Calc'd:	C, 43.59;	H, 7.58;	N, 10.89
Found:	C, 43.47;	H, 7.08;	N, 10.57

(R)-[1-Methyl-2-[4-(2-methoxyphenyl)-1-piperazinyl]ethylamine (2.49 g, 0.01 mol) and 1-methylcyclohexane carboxylic acid (2.84 g, 0.02 mol) in 25 mL of CH_2Cl_2 were chilled in ice and treated with diethylcyanophosphonate (3.26 g, 3.1 mL, 0.02 mol) in 10 mL of CH_2Cl_2 over 15 minutes followed by N-methyl morpholine (2.02 g, 2.2 mL, 0.02 mol) in 10 mL of CH_2Cl_2 over 15 minutes. After stirring overnight, the solution was washed with 2N NaOH (2 x 50 mL), water (2 x 50 mL) and dried (anhydrous K_2CO_3). The product was isolated using dry column chromatography on silica gel (300 g) and development with ethyl acetate. The product (R_f 0.59 uniplatte, ethyl acetate) was dissolved in 150 mL of diethyl ether and precipitated with 4.5 N HCl in ethyl acetate. Recrystallization from methanol/diethyl ether gave the pure title compound as the dihydrochloride, mp. 180-185°C, $[\alpha]_D^{25} -9.32^\circ c = 1.09$ MeOH.

Elemental analysis for $C_{22}H_{35}N_3O_2 \cdot 2HCl$			
Calc'd:	C, 59.18;	H, 8.35;	N, 9.41
Found:	C, 58.90;	H, 8.21;	N, 9.04

Example 21

(R)-1-Methyl-N-[1-methyl-2-[4-(2-pyrimidinyl)]-1-piperazinyl]ethyl]cyclohexane carboxamide

In a manner analagous to Example 20 using t-butoxycarbonyl-D-alanine and 1-benzylpiperazine, (R)-1-methyl-2-[4-phenylmethyl-1-piperazinyl]ethyl amine was obtained as an oil. A sample was converted to the trihydrochloride, dihydrate, mp. 246-248°C.

Elemental analysis for $C_{14}H_{23}N_3 \cdot 3HCl \cdot 2H_2O$			
Calc'd:	C, 44.39;	H, 7.92;	N, 11.09
Found:	C, 44.43;	H, 6.89;	N, 10.71

In a manner analagous to Example 20 using (R)-1-methyl-2-[4-phenylmethyl-1-piperazinyl]ethylamine and 1-methylcyclohexanecarboxylic acid, (R)-1-methyl-N-[1-methyl-2-[[4-phenylmethyl-1-piperazinyl]ethyl]-cyclohexanecarboxamide was obtained after crystallization from methanol and diethyl ether, mp. 168-170°C, $[\alpha]^{25}_{D} -8.85$ c = 1.02 MeOH.

Elemental analysis for $C_{22}H_{35}N_{30} \cdot 2HCl \cdot 11/2 H_2O$			
Calc'd:	C, 57.75;	H, 8.81;	N, 9.18
Found:	C, 57.73;	H, 8.76;	N, 9.19

The product from the preceding paragraph (6.91g, 0.0151 mol) and 10% palladium on carbon (1 g) were shaken in 95% ethanol (200 mL) on a Parr hydrogenation apparatus until hydrogen uptake stopped and TLC on a sample of base showed no starting material (20 hours). The catalyst was removed by filtration and the filtrate was evaporated to dryness. The solid together with 2-chloropyrimidine (1.81 g, 0.0158 mol), powdered anhydrous potassium carbonate (20.7 g, 0.15 mol) and triethylamine (1 mL) were stirred at 65-70°C in dimethylformamide (100 mL) overnight. The solvent was removed on a Rotovapor and the residue was partitioned between water and dichloromethane. The organic layer was washed with water, dried over sodium sulfate and evaporated. The title compound crystallized from hexane. Yield 2.58 g 49.4%, mp. 96.98°C, $[\alpha]^{25}_{D} -22.9$ c = 1.00 MeOH.

Elemental analysis for $C_{19}H_{31}N_{50}$			
Calc'd:	C, 66.05;	H, 9.04;	N, 20.2
Found:	C, 65.86;	H, 9.43;	N, 19.92

Example 22

N-(1,1-Dimethylethyl)-3-[4-(2-methoxyphenyl)-1-piperazinyl]propanamide

A solution of N-tert-butylacrylamide (1.799 g, 14.2 mmol) and 1-(2-methoxyphenyl)piperazine (2.111 g, 11.0 mmol) in propanol (20 mL) was maintained at room temperature for 8 days, evaporated in *vacuo*, and chromatographed [silica; ethanol-ethyl acetate (1:20)] to give the free base of the product as a yellow oil (2.52 g, 72%).

The oil was dissolved in propan-2-ol (10 mL) and the solution acidified with ethereal hydrogen chloride. The mixture was evaporated in *vacuo* and the precipitate washed with diethyl ether to give the product as the dihydrochloride quarter hydrate (2.36 g, mp. 245-248° C (dec)).

Elemental analysis for $C_{18}H_{29}N_3O_2 \cdot 2HCl \cdot 1/4 H_2O$			
Calc'd:	C, 54.5;	H, 8.0;	N, 10.6
Found:	C, 54.9;	H, 8.1;	N, 10.5

Example 23

2,2-Dimethylpropanoic acid 2-(4-(2-methoxyphenyl)piperazin-1-yl)-1-phenylethyl ester

A solution of 2,2-dimethylpropanoic acid chloride (0.28 g, 2.34 mmoles) in dichloromethane (10 mL) was added dropwise to a stirred solution of 2-(4-(2-methoxyphenyl)piperazin-1-yl)-1-phenylethanol dihydrochloride (0.90 g, 2.34 mmoles) and triethylamine (0.73 g, 7.2 mmoles) in dichloromethane (15.0 mL). The reaction mixture was stirred at room temperature over the weekend and a further quantity of the same acid chloride (0.14 g, 1.17 mmoles) and triethylamine (0.30 g, 1.17 mmoles) was added. The reaction mixture was stirred overnight, filtered, concentrated under reduced pressure and chromatographed on silica gel. Elution with hexane:ethyl acetate (2:1) afforded an oil which was dissolved in acetonitrile and acidified with ethereal hydrogen chloride to give colourless crystals of the title compound as the dihydrochloride (0.91 g), mp. 237.9-240.9° C (dec).

Elemental analysis for $C_{24}H_{32}N_2O_3 \cdot 2HCl$			
Calc'd:	C, 61.4;	H, 7.3;	N, 6.0
Found:	C, 61.1;	H, 7.4;	N, 6.3

Example 24

0-(2-(4-(2-Methoxyphenyl)piperazin-1-yl)ethyl)-N-(2-methyl-2-propyl)carbamate

Tributyltin methoxide (0.05 ml, 0.20 mmoles) was added to a solution of 2-(4-(2-methoxyphenyl)-piperazin-1-yl)-1-phenyl-ethanol (1.50 g, 4.8 mmoles) and t-butyl isocyanate (0.52 g, 5.3 mmoles) in toluene (15.0 mL). The reaction mixture was stirred for two days at room temperature and then chromatographed on silica gel, gradient eluting with hexane:ethyl acetate (2:1 to 1:2) to afford a colourless low-melting solid (1.93 g) which solidified on standing. The crude product was dissolved in ethyl acetate and acidified with ethereal hydrogen chloride to afford a colourless powder of the title compound as the dihydrochloride (1.63 g), mp. 184.3-188.3 °C.

Elemental analysis for $C_{24}H_{33}N_3O_3 \cdot 2HCl$			
Calc'd:	C, 59.4;	H, 7.5;	N, 8.7
Found:	C, 59.8;	H, 7.5;	N, 8.7

Example 25

N-Tert-butyl-2-methoxyphenyl-3-(4-(2-methoxyphenyl)piperazin-1-yl)propanamide

A solution of potassium tert-butoxide (5.15 g, 46.0 mmols) in warm tert-butanol (21 ml) was added to a cooled (ice-methanol) suspension of 1-(2-[2-methoxyphenyl]-2-oxo)ethyl-4-(2-methoxyphenyl)piperazine dihydrochloride (5.00 gm, 12.11 mmols) and tosylmethylisocyanide (2.60 g, 13.31 mmols) in dry dimethoxyethane (100 mL). The reaction mixture was slowly allowed to warm to room temperature over 2 hours. Acetic acid (0.80 g, 13.33 mmols) was added to the reaction mixture followed by the addition of ethyl acetate (200 mL). The precipitate formed was filtered off and the filtrate concentrated to about 50 mL under reduced pressure. The concentrate was dissolved in water and washed with ethyl acetate. The combined organic phases were washed with brine, water, dried ($MgSO_4$) and concentrated to afford a brown oil. The crude product was chromatographed on silica gel and gradient eluted with hexane:ethyl acetate (3:2) to ethyl acetate, to afford a brown oil (3.30 g). A sample (1.0 g) of the oil was dissolved in diisopropylether and acidified with ethereal hydrogen chloride to afford off-white crystals which were recrystallized from diethyl-ether in methanol to give 2-(2-methoxyphenyl)-3-(4-(2-methoxyphenyl)-piperazin-1-yl)propanenitrile as a dihydrochloride quarterhydrate as colourless crystals (0.75 g), mp. 189-192 °C.

Elemental analysis for $C_{21}H_{25}N_3O_2 \cdot 2HCl \cdot 1/4H_2O$			
Calc'd:	C, 58.9;	H, 6.5;	N, 9.8
Found:	C, 58.7;	H, 6.5;	N, 9.5

Tert-butanol (1.20 g, 16.2 mmoles) was added to an ice-cooled solution of 2-(2-methoxyphenyl)-3-(4-(2-methoxyphenyl)piperazin-1-yl)propanenitrile dihydrochloride (1.90 g, 5.41 mmoles) in methane sulphonic acid (10.0 mL) and the reaction mixture stirred at room temperature for 48 hours. The reaction mixture was poured onto ice and basified with a mixture of 2M sodium hydroxide and solid sodium hydroxide. The aqueous layer was washed with ethyl acetate (3 x 30 mL) and the combined organic phases washed with brine (30 mL), water (30 mL), dried ($MgSO_4$) and concentrated to afford a brown oil. The crude product was chromatographed on silica gel and gradient eluted with ethyl acetate:hexane (1:1 to 4:1) and finally ethyl acetate to give a brown oil (2.06 g) which solidified on standing. The crude product was dissolved in diethyl ether and acidified with ethereal hydrogen chloride to afford a powder which was triturated in diisopropylether and then recrystallised from a mixture of diisopropyl ether and ethanol to afford the title compound as a dihydrochloride hydrate (0.30 g), mp. 129.0-132.5 °C.

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Elemental analysis for $C_{25}H_{35}N_3O_3 \cdot 2HCl \cdot H_2O$			
Calc'd:	C, 58.1;	H, 7.6;	N, 8.1
Found:	C, 58.5;	H, 7.9;	N, 7.7

Example 26

N-Tert-butyl-3-[1-[4-(2-methoxy)phenyl]piperaziny]-2-phenylpropionhydrazide

A suspension of tert-butylhydrazine hydrochloride (0.63 g, 5.0 mmol) in dry tetrahydrofuran (20 mL) was treated with triethylamine (0.7 mL, 5.0 mmol). To the suspension were added 3-[1-[4-(2-methoxy)phenyl]piperaziny]-2-phenylpropionic acid (1.70 g, 5.0 mmol) and N,N-dicyclohexylcarbodiimide (1.03 g, 5.0 mmol) and the mixture was stirred at room temperature for 18 hours. The mixture was concentrated in vacuo and the residue was extracted with hot ethyl acetate (50 mL). The precipitate was filtered off and washed, and the filtrate was concentrated in vacuo. The product was chromatographed on silica with eluant ethyl acetate:toluene, 1:4/ethyl acetate to give the title compound as the free base (0.79 g), which was dissolved in ethyl acetate (40 mL) to give a solution. This was acidified with ethereal hydrogen chloride (5 mL) to give a precipitate which was triturated with acetonitrile to give the title compound as the dihydrochloride trihydrate (0.56 g), mp. 208-210° C.

Elemental analysis for $C_{24}H_{34}N_4O_2 \cdot 2HCl \cdot 3H_2O$			
Calc'd:	C, 53.6;	H, 7.9;	N, 10.49
Found:	C, 53.7;	H, 7.6;	N, 10.2

Example 27

O-Tert-butyl-3-[1-[4-(2-methoxy)phenyl]piperaziny]-2-phenylpropionohydroxamate

A stirred suspension of O-tert-butylhydroxylamine hydrochloride (628 mg, 5.0 mmol) in dry tetrahydrofuran (20 mL) was treated successively with triethylamine (1.4 mL, 10 mmol), and 3-[1-[4-(2-methoxy)phenyl]piperaziny]-2-phenylpropionic acid (1.70 g, 5.0 mmol). A solution of dicyclohexylcarbodiimide (1.03 g, 5.0 mmol) in dry tetrahydrofuran (5 mL) was added, and the mixture was stirred for 2 hours and was allowed to stand for 81 hours. The suspension was concentrated in vacuo and extracted with hot ethyl acetate (2 x 40 mL). The extracts were concentrated in vacuo and the residue chromatographed on silica with eluant ethyl acetate:toluene 1:4/ethyl acetate to give the title compound as the free base (1.39 g). The product was dissolved in methanol (70 mL), and the solution was acidified with ethereal hydrogen chloride (5 mL), concentrated in vacuo and the product triturated with acetonitrile to give the title compound as the dihydrochloride (512 mg), mp. 188° C (dec).

Elemental analysis for $C_{24}H_{33}N_3O_3 \cdot 2HCl \cdot 2H_2O$			
Calc'd:	C, 57.4;	H, 7.4;	N, 8.4
Found:	C, 57.6;	H, 7.4;	N, 8.35

Example 28

(R*)- and (S*)-N-Tertiary butyl-3-[4-(2-methoxy)phenyl]piperazin-1-yl]-2-phenylpropionamide

A solution of di-p-toluoyl-L-tartaric acid monohydrate (4.67 g, 11.55 mmol) in acetonitrile (20 ml) was added in one portion to a solution of compound of Example 13, free base (4.57 g, 11.55 mmol) in acetonitrile (80 ml). The solution was concentrated in vacuo to give a white crystalline residue, which was redissolved in boiling acetonitrile (100 ml). The solution was allowed to cool overnight. The bulk solution was filtered, and the remaining crystals were collected, to give the first enantiomer as its di-p-toluoyl-L-tartrate (4.63 g). During the collection of the first crop of crystals, crystallisation was observed in the filtrate, and a second crop of crystals was collected separately, to give the second enantiomer as its di-p-toluoyl-L-tartrate (2.86 g). The remaining filtrate was concentrated in vacuo to give a foam (1.48 g). The di-p-toluoyl-L-tartrate of the first enantiomer was combined with the foam, and the mixture was recrystallised twice from the hot acetonitrile (100 ml) to give the (R*) title compound as its di-p-toluoyl-L-tartrate (3.64 g), m.p. 130° - 145° C (dec.).

Elemental analysis for $C_{24}H_{33}N_3O_2 \cdot C_{20}H_{18}O_8 \cdot 0.25 H_2O$			
Calc'd:	C, 67.2;	H, 6.6;	N, 5.3
Found:	C, 67.0;	H, 6.8;	N, 5.3

The di-p-toluoyl-L-tartrate of the second enantiomer was combined with the two residues of recrystallisation of the di-p-toluoyl-L-tartrate of the first enantiomer, and the mixture was dissolved in chloroform (50 ml). The solution was washed with N aqueous sodium hydroxide (60 ml), and the aqueous phase was extracted with chloroform (50 ml). The combined chloroform phases were dried (Na_2SO_4), and concentrated in vacuo to give a white solid (2.50 g). The solid was dissolved in acetonitrile (25 ml), and a solution of di-p-toluoyl-L-tartaric acid (2.56 g, 6.32 mmol) in acetonitrile (5 ml) was added. The solution was concentrated in vacuo to give a solid residue, which was treated with acetonitrile (20 ml) and heated. During heating, crystallisation was observed, and the mixture was allowed to stand overnight. The product was collected to give the (S*)-title compound as its di-p-toluoyl-L-tartrate (4.08 g), 140° - 145° C (dec.).

Elemental analysis for $C_{24}H_{33}N_3O_2C_{20}H_{18}O_5 \cdot 0.25 H_2O$			
Calc'd:	C, 67.2;	H, 6.6;	N, 5.3
Found:	C, 67.1;	H, 6.6;	N, 5.3

The di-p-toluoyl-L-tartrate of the (R*)-title compound was dissolved in chloroform (50 ml), and the solution was washed with N aqueous sodium hydroxide (60 ml). The aqueous phase was extracted with chloroform (50 ml), and the combined chloroform phases were dried (Na_2SO_4), and concentrated in vacuo to give the (R*)-title compound as the free base, $[a]_D^{24} - 7.4^\circ C$ (c, 0.65 in $CHCl_3$). The free base was dissolved in ethyl acetate (90 ml) and the solution was acidified with ethereal hydrogen chloride (5 ml). The

mixture was concentrated in vacuo, and the residue was triturated with hot acetonitrile (100 ml), to give the (R*)-title compound as the dihydrochloride (1.79 g, 76% overall) m.p. 200°-215° C (dec.), $[\alpha]_D^{24} + 42^\circ$ C (c. 1.1 in MeOH-H₂O, 1:7).

Elemental analysis for C ₂₄ H ₃₃ N ₃ O ₂ • 2 HCl			
Calc'd:	C, 61.5;	H, 7.5;	N, 9.0
Found:	C, 61.8;	H, 7.5;	N, 9.0

The di-p-toluoyl-L-tartrate of the (S*)-title compound was treated in the same way as the di-p-toluoyl-L-tartrate of the (R*)-title compound, to give the (S*)-title compound as the free base, $[\alpha]_D^{24} + 8^\circ$ C (c. 0.55 in CHCl₃). The free base was converted to its dihydrochloride with the same procedure used above to give the (S*)-title compound as the dihydrochloride (2.03 g, 86% overall), m.p. 200°-215° C (dec.), $[\alpha]_D^{24} - 44^\circ$ C (c. 1.1 in MeOH-H₂O, 1:7).

Elemental analysis for C ₂₄ H ₃₃ N ₃ O ₂ • 2 HCl			
Calc'd:	C, 61.5;	H, 7.5;	N, 9.0
Found:	C, 61.3;	H, 7.3;	N, 8.9

The compounds of this invention have been demonstrated to possess 5HT_{1A} receptor binding properties which characterize them as useful anxiolytic and/or antidepressant agents. Where the compounds of this invention also display D₂ receptor site binding properties, they also have an anti-psychotic element which is of use in treatment of anxiety, depression, senile dementia (SDAT), Huntington's chorea, stroke and sexual disturbances.

Those compounds in which R⁵ is alkyl of 4 to 8 carbon atoms or optionally substituted phenyl or benzyl, selectively bind to receptors of the 5-HT_{1A} type to a much greater extent than they bind to other receptors such as α₁ and D₂ receptors.

The pharmacological profile of the compounds of this invention resembles that of buspirone obtained by measuring the compound's ability to displace [³H] 8-OH DPAT (dipropylaminotetralin) from the 5-HT_{1A} serotonin receptor by the procedure of Hall *et al.*, J. Neurochem. 44: 1685-1696, 1985. The compounds of this invention, like buspirone, exhibited potent affinity for this serotonin receptor subtype. The anxiolytic activity of buspirone is currently believed to be due, at least in part, to this receptor (Vander Maclen *et al.*, Eur. J. Pharmacol. 1986, 129 (1-2) 123-130.

The D₂ dopamine receptor binding study was in accordance with a modification of the procedure of Field *et al.*, Brain Res., 136, pp. 578-584 (1977) and Yamamura *et al.*, eds., Neurotransmitter Receptor Binding, Raven Press, N.Y. (1978), wherein homogenized limbic brain tissue is incubated with ³H - spiroperiodol and various concentrations of test compounds, filtered and washed and shaken with Hydrofluoro scintillation cocktail (National Diagnostics) and counted in a Packard 460CD scintillation counter. The test results of these studies are as follows:

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	<u>Compound of</u>	<u>Affinity for 5HT_{1A}</u> <u>Receptor % Inhibition</u>	<u>Affinity for D₂</u> <u>Receptor % Inhibition</u>
5	Example 1	91 at 0.1 μ M	
	Example 2	100 at 0.1 μ M	
	Example 3	86 at 1 μ M	89 at 1 μ M
	Example 4	98 at 1 μ M	99 at 1 μ M
10	Example 5	98 at 1 μ M	58 at 1 μ M
	Example 12	IC ₅₀ 11.8 nM	
15		98 at 1 μ M	
		86 at 0.1 μ M	
20	Example 13	IC ₅₀ 25.0 nM	IC ₅₀ 1740 nM
		86 at 1 μ M	32 at 1 μ M
		69 at 0.1 μ M	8 at 0.1 μ M
25	Example 14	IC ₅₀ 11.4 nM	38 at 10 μ M
		Affinity for 5HT _{1A}	Affinity for D ₂
30			
35			
40			
45			
50			
55			

	<u>Compound of</u>	<u>Receptor % Inhibition</u>	<u>Receptor % Inhibition</u>
5		100 at 1 μ M	90 at 0.1 μ M
	Example 15	98 at 0.1 μ M	
10	Example 16	56 at 0.1 μ M	
	Example 18	85 at 0.1 μ M	
	Example 19	67 at 0.1 μ M	
15	Example 20	100 at 0.1 μ M	
	Example 22	IC ₅₀ 287.0 nM	
20		72 at 1 μ M	18 at 0.1 μ M
	Example 23	IC ₅₀ 270.0 nM	
25		78 at 1 μ M	27 at 0.1 μ M
	Example 24	IC ₅₀ 20.0 nM	
30		97 at 1 μ M	73 at 0.1 μ M
	Example 26	IC ₅₀ 118.0 nM	
35		96 at 1 μ M	48 at 0.1 μ M

40 The very weak D₂ receptor binding exhibited by the compounds of Examples 13 and 14 illustrate the selective 5HT_{1A} receptor binding properties of those compounds mentioned, supra, where R⁵ is alkyl of 4 to 8 carbon atoms or an optionally substituted phenyl or benzyl moiety.

45 Hence, the compounds of this invention are anxiolytic and/or antidepressant agents useful in the treatment of depression and in alleviating anxiety and in those instances where meaningful D₂ binding occurs as antipsychotic agents for treatment of psychoses such as paranoia and schizophrenia, as well as the related secondary conditions of sexual dysfunction, senile dementia (SDAT) and the like. As such, the compounds may be administered neat or with a pharmaceutical carrier to a patient in need thereof. The pharmaceutical carrier may be solid or liquid.

50 A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, s-lubilizers, suspending agents, filters, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired.

55 The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellants.

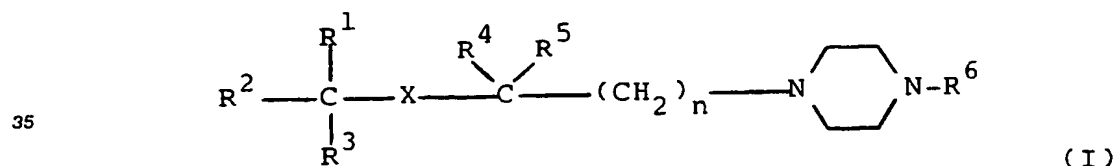
Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. When the compound is orally active, it can be administered orally either in liquid or solid composition form.

Preferably, the pharmaceutical composition is in unit dosage form, e.g., as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

The dosage to be used in the treatment of a specific psychosis must be subjectively determined by the attending physician. The variables involved include the specific psychosis of state of anxiety and the size, age and response of the patient.

Claims

1. A compound of the formula:



in which

R¹ is alkyl of 1 to 6 carbon atoms;

R² and R³ are alkyl of 1 to 6 carbon atoms or taken together they are polymethylene of 2 to 12 carbon atoms or taken together with the carbon atom to which they are attached, R² and R³ complete a 5-norbornen-2-yl moiety;

X is -CO₂-, -OCO-, -OCO₂-, -N(R⁷)CO-, -NHNHCO-, -ON(R⁷)CO-, -CON(R⁷)-, N(R⁷)CO₂-, -OCON(R⁷)- or -N-(R⁷)CON(R⁸)-; wherein R⁷ and R⁸ are, independently, hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, benzyl, substituted phenyl or substituted benzyl in which the substituents are halo, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, cyano, nitro or perhalomethyl;

R⁴ is hydrogen or alkyl of 1 to 6 carbon atoms;

R⁵ is hydrogen, alkyl of 1 to 8 carbon atoms, hydroxyalkyl of 1 to 3 carbon atoms, phenyl, benzyl, substituted phenyl or substituted benzyl in which the substituents are hydroxy, halo, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, trifluoromethyl, nitro, cyano, carbalkoxy of 2 to 7 carbon atoms, carboxamido, amino, alkylamino of 1 to 6 carbon atoms or dialkylamino of 2 to 12 carbon atoms;

R⁶ is phenyl, benzyl, 2-, 3-, or 4-pyridinyl, 2-pyrimidinyl or 2-pyrazinyl; any of which may be substituted by one or more hydroxy, halo, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, trifluoromethyl, nitro, cyano, carbalkoxy of 2 to 7 carbon atoms, carboxamido, amino, alkylamino of 1 to 6 carbon atoms or dialkylamino of 2 to 12 carbon atoms;

and

n is one of the integers 1, 2, 3, 4 or 5; or a pharmaceutically acceptable salt thereof, with the proviso that

when X is -CON(R⁷)- and R⁷ is alkyl, R⁶ is other than 2-pyrimidinyl.

2. A compound as claimed in claim 1 in which

R² and R³ are alkyl of 1 to 6 carbon atoms or taken together they are polymethylene of 2 to 6 carbon atoms or taken together with the carbon atom to which they are attached, R² and R³ complete a 5-norbornen-2-yl moiety;

R⁵ is hydrogen, alkyl of 1 to 6 carbon atoms, hydroxyalkyl of 1 to 3 carbon atoms, phenyl, benzyl, p-hydroxyphenyl, p-methoxyphenyl, o-methoxyphenyl, p-chlorophenyl or p-fluorophenyl;

and

R⁶ is phenyl, 2-alkylphenyl in which the alkyl substituent has 1 to 6 carbon atoms, 2-alkoxyphenyl in which the alkoxy substituent has 1 to 6 carbon atoms, 2-halophenyl, 2-cyanophenyl, 2-nitrophenyl, 2-perhalomethylphenyl, benzyl, 2-, 3- or 4-pyridinyl, 2-pyrimidinyl or 2-pyrazinyl;

or a pharmaceutically acceptable salt thereof, with the proviso that when X is -CON(R⁷)- and R⁷ is alkyl, R⁶ is other than 2-pyrimidinyl.

3. A compound of Claim 2 in which R⁶ is 2-, 3- or 4-pyridinyl, 2-pyrimidinyl or 2-pyrazinyl, R¹, R² and R³ are methyl, R⁴ and R⁵ are hydrogen, X is -CO₂ - or -NHCO₂, and n is 2.

4. A compound of Claim 2 in which R⁶ is 2-methoxyphenyl, 2-chlorophenyl or 2-pyrimidinyl.

5. A compound as claimed in Claim 1 in which R² and R³ are, independently, alkyl of 1 to 6 carbon atoms.

6. A compound of Claim 1 in which R² and R³ are tetramethylene, pentamethylene or hexamethylene.

7. A compound of as claimed in any one of Claims 1, 5 or 6 in which R⁴ is hydrogen and R⁵ is alkyl of 1 to 6 carbon atoms, phenyl or benzyl.

8. A compound of as claimed in any one of Claims 1, 5, 6 or 7 in which R⁶ is 2-methoxyphenyl, 2-chlorophenyl or 2-pyrimidinyl.

9. A compound as claimed in Claim 1 in which R⁵ is alkyl or 4 to 8 carbon atoms, phenyl, benzyl, substituted phenyl or benzyl in which the substituents are halo, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, trifluoromethyl, nitro, cyano, carbalkoxy of 2 to 7 carbon atoms, carboxamido, alkylamino of 1 to 6 carbon atoms or dialkylamino of 2 to 12 carbon atoms.

10. A compound as claimed in claim 9 in which X is N(R⁷)CO or -OCO, where R⁷ is hydrogen or alkyl of 1 to 6 carbon atoms, n is 1 and R² and R³ are, independently, alkyl of 1 to 6 carbon atoms.

11. The compound of Claim 1 which is N-(1,1-dimethylethyl)-N¹-[4-[4-(2-methoxyphenyl)-1-piperazinyl]-butyl]urea, or a pharmaceutically acceptable salt thereof, or

N-[4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl-2,2-dimethylpropanamide, or a pharmaceutically acceptable salt thereof, or

2,2-dimethylpropanoic acid 2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl ester, or a pharmaceutically acceptable salt thereof, or

2,2-dimethylpropanoic acid 3-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl ester, or a pharmaceutically acceptable salt thereof, or

2,2-dimethylpropanoic acid 3-[4-(2-chlorophenyl)-1-piperazinyl]ethyl ester, or a pharmaceutically acceptable salt thereof, or

2,2-dimethylpropanoic acid 3-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl ester, or a pharmaceutically acceptable salt thereof, or

(R)-N-[1-methyl-2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl trimethylacetamide, or a pharmaceutically acceptable salt thereof, or

N-2-(4-(2-methoxyphenyl)-1-piperazine)ethyl 2,2-dimethylpropanamide or a pharmaceutically acceptable salt thereof, or

N-(1,1-dimethylethyl)-4-(2-methoxyphenyl)-1-piperazine acetamide, or a pharmaceutically acceptable salt thereof, or

N-[1,1-dimethylethyl)-4-(2-pyrimidinyl)-1-piperazinepropanamide, or a pharmaceutically acceptable salt thereof, or

2,2-dimethylpropanoic acid 2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl ether, or a pharmaceutically acceptable salt thereof, or

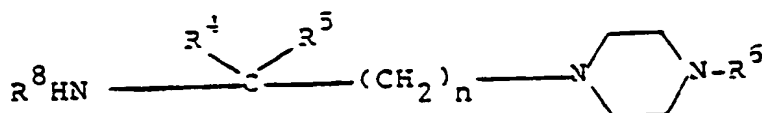
tertiary-butyl 3-[1-[4-(2-methoxyphenyl)piperazinyl]-2-phenylpropanoate, or a pharmaceutically acceptable salt thereof, or

N-tertiary-butyl 3-[4-(2-methoxyphenyl)piperazinyl]-2-phenylpropanamide, or a pharmaceutically acceptable salt thereof, or

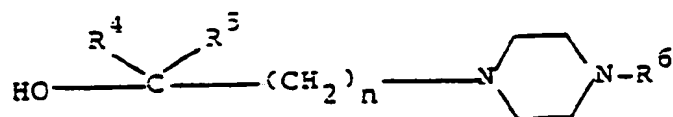
N-tertiary-butyl 2-[[4-(2-methoxyphenyl)piperazinyl]methyl]-3-phenylpropanamide, or a pharmaceutically acceptable salt thereof, or

N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-1-methylcyclohexanecarboxamide, or a pharmaceutically acceptable salt thereof.

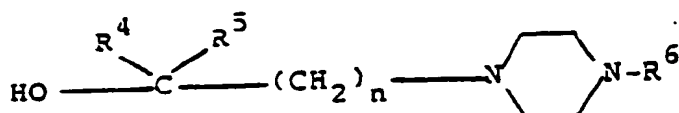
- ceptable salt thereof, or
 4-(2-methoxyphenyl)-N-(1-methylcyclohexyl)-1-piperazinepropanamide, or a pharmaceutically acceptable salt thereof, or
 4-(2-pyrimidinyl)-N-(1-methylcyclohexyl)-1-piperazinepropanamide, or a pharmaceutically acceptable salt thereof, or
 5 N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(1-methylcyclohexyl)urea, or a pharmaceutically acceptable salt thereof, or
 N-2-(4-[2-pyrimidinyl]-1-piperazinyl)ethyl-1-methylcyclohexylcarboxamide, or a pharmaceutically acceptable salt thereof, or
 10 (R)-N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]-1-methylethyl]-1-methylcyclohexane carboxamide, or a pharmaceutically acceptable salt thereof, or
 (R)-1-methyl-N-[1-methyl-2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]cyclohexane carboxamide, or a pharmaceutically acceptable salt thereof, or
 N-(1,1-dimethylethyl)-3-[4-(2-methoxyphenyl)-1-piperazinyl]-propanamide, or a pharmaceutically acceptable salt thereof, or
 15 2,2-dimethylpropanoic acid 2-(4-[2-methoxyphenyl]piperazin-1-yl)-1-phenylethyl ester, or a pharmaceutically acceptable salt thereof, or
 O-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)-N-(2-methyl-2-propyl)carbamate, or a pharmaceutically acceptable salt thereof, or
 20 N-tert-butyl-2-methoxyphenyl-3-(4-(2-methoxyphenyl)-piperazin-1-yl)propanamide, or a pharmaceutically acceptable salt thereof, or
 N-tert-butyl-3-[1-[4-(2-methoxy)phenyl]piperazinyl]-2-phenyl-propionhydrazide, or a pharmaceutically acceptable salt thereof, or
 O-tert-butyl-3-[1-(4-(2-methoxy)phenyl)piperazinyl]-2-phenyl-propionhydroxamate, or a pharmaceutically acceptable salt thereof, or
 25 (R*)-N-tertiary butyl-3-[4-(2-methoxy)phenyl]piperazin-1-yl]-2-phenylpropionamide, or a pharmaceutically acceptable salt thereof, or
 (S*)-N-tertiary butyl-3-[4-(2-methoxy)phenyl]piperazin-1-yl]-2-phenylpropionamide, or a pharmaceutically acceptable salt thereof.
12. A process for preparing a compound claimed in Claim 1 which comprises:
 30 (a) reacting an amine of formula



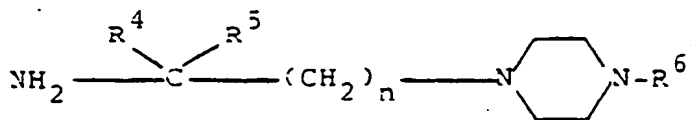
or an alcohol of formula



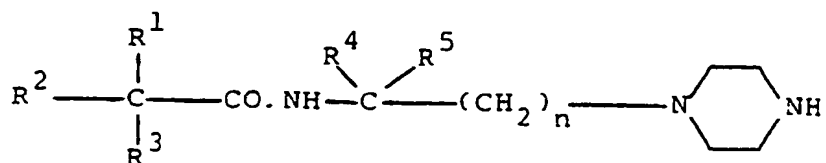
with an appropriate isocyanate to give a urea or carbamate derivative, or
 (b) esterifying an alcohol of formula



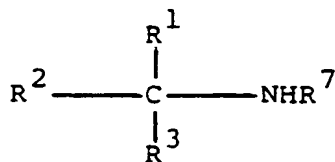
to give an ester derivative or
 (c) acylating an amine of formula



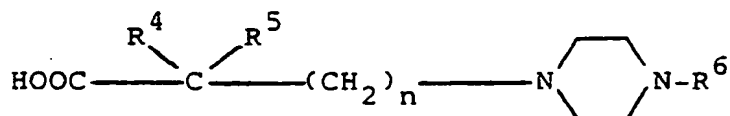
to give a carboxamide derivative or
(d) alkylating a compound of formula



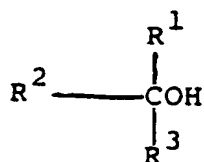
or
(e) acylating an amine of formula



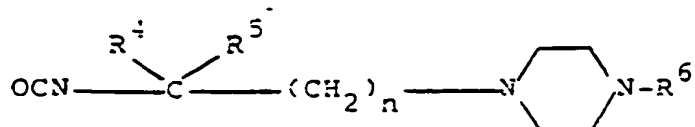
with an acid of formula



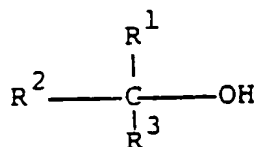
or with an acylating derivative thereof or esterifying the acid with an alcohol of formula



or
(f) reacting a piperazine isocyanate of formula

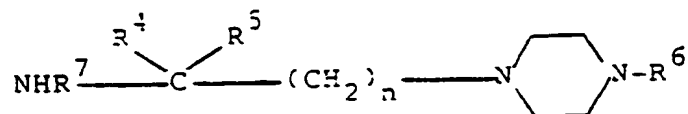


with an alcohol of formula

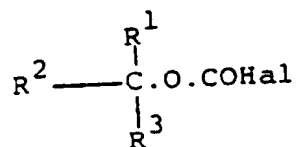


or

(g) reacting a piperazinylalkylamine of formula

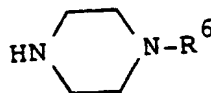


with a compound of formula

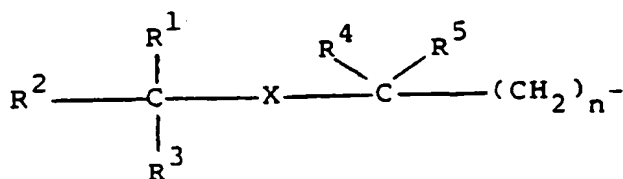


(where Hal is halogen) or

(h) alkylating a piperazine of formula

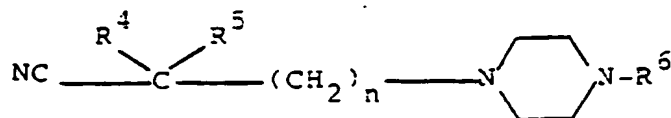


with an alkylating agent providing the group

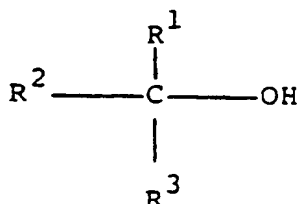


or

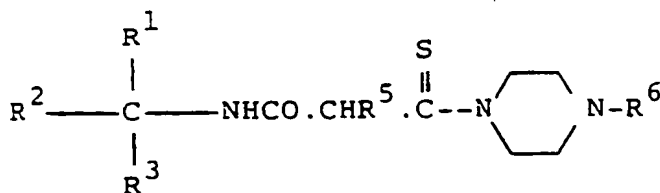
(i) reacting a nitrile of formula



with a tertiary alcohol of formula



- under acidic conditions or
 (j) desulphurising a sulphur containing compound of formula



or

- (k) converting a free base of formula (I) into a pharmaceutically acceptable salt thereof.

or

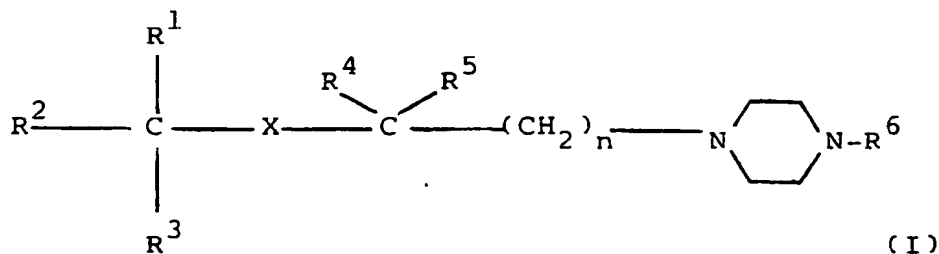
- (l) resolving a racemic compound of formula (I) to give an enantiomer.

13. A pharmaceutical composition comprising a compound claimed in any one of claims 1 to 11 in association with a pharmaceutically acceptable carrier.

14. A compound as described in any one of claims 1 to 11 for use as a pharmaceutical.

Claims for the following Contracting States: ES,GR

1. A process for preparing a compound of the formula:



in which

R¹ is alkyl of 1 to 6 carbon atoms;

R² and R³ are alkyl of 1 to 6 carbon atoms or taken together they are polymethylene of 2 to 12 carbon atoms or taken together with the carbon atom to which they are attached, R² and R³ complete a 5-norbornen-2-yl moiety;

X is -CO₂-, -OCO-, -OCO₂-, -N(R⁷)CO-, -NHNHCO-, -ON(R⁷)CO-, -CON(R⁷)-, N(R⁷)CO₂-, -OCON(R⁷)- or -N-(R⁷)CON(R⁸)-; wherein R⁷ and R⁸ are, independently, hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, benzyl, substituted phenyl or substituted benzyl in which the substituents are halo, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, cyano, nitro or perhalomethyl;

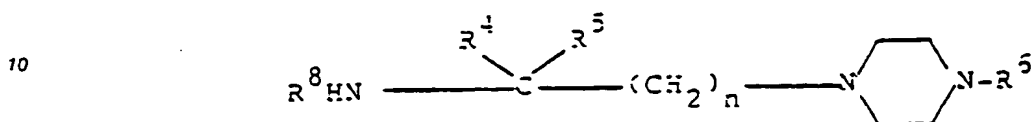
R⁴ is hydrogen or alkyl of 1 to 6 carbon atoms;

R⁵ is hydrogen, alkyl of 1 to 8 carbon atoms, hydroxyalkyl of 1 to 3 carbon atoms, phenyl, benzyl, substituted phenyl or substituted benzyl in which the substituents are hydroxy, halo, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, trifluoromethyl, nitro, cyano, carbalkoxy of 2 to 7 carbon atoms, carboxamido, amino, alkylamino of 1 to 6 carbon atoms or dialkylamino of 2 to 12 carbon atoms;

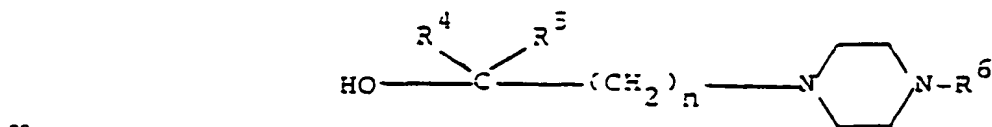
R⁶ is phenyl, benzyl, 2-, 3-, or 4-pyridinyl, 2-pyrimidinyl or 2-pyrazinyl; any of which may be substituted by

one or more hydroxy, halo, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, trifluormethyl, nitro, cyano, carbalkoxy of 2 to 7 carbon atoms, carboxamido, amino, alkylamino of 1 to 6 carbon atoms or dialkylamino of 2 to 12 carbon atoms;
and

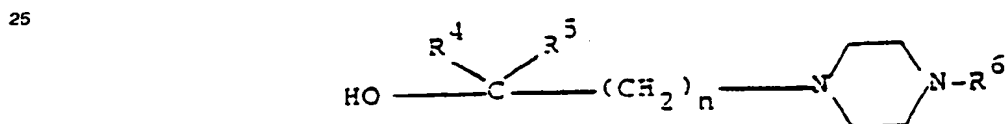
- 5 n is one of the integers 1, 2, 3, 4 or 5; or a pharmaceutically acceptable salt thereof, with the proviso that when X is -CON(R⁷)- and R⁶ is other than 2-pyrimidinyl, which process comprises
(a) reacting an amine of formula



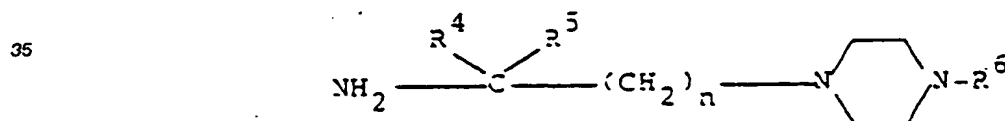
- 15 or an alcohol of formula



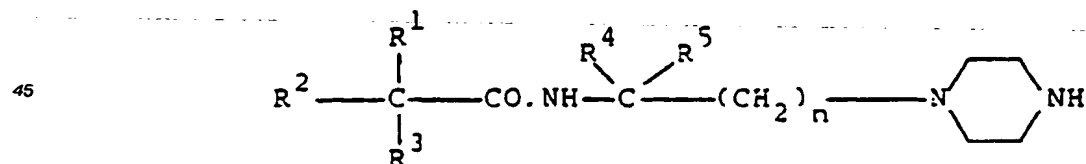
- with an appropriate isocyanate to give a urea or carbamate derivative, or
(b) esterifying an alcohol of formula



- 30 to give an ester derivative or
(c) acylating an amine of formula



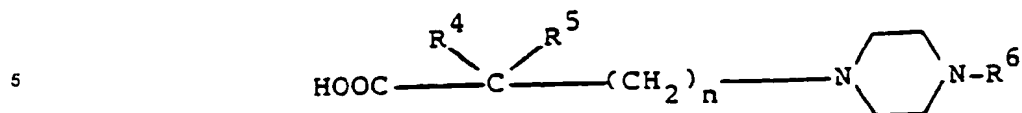
- 40 to give a carboxamide derivative or
(d) alkylating a compound of formula



- 50 or
(e) acylating an amine of formula



with an acid of formula

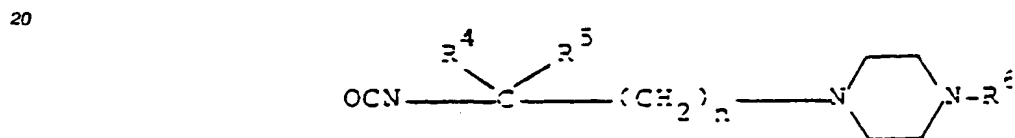


or with an acylating derivative thereof or esterifying the acid with an alcohol of formula



or

(f) reacting a piperazine isocyanate of formula

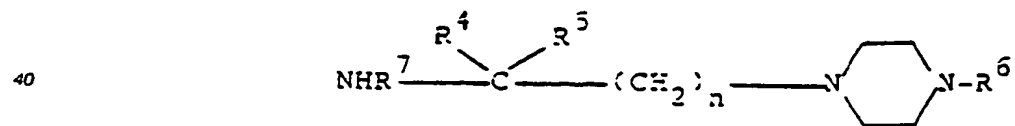


with an alcohol of formula



35 or

(g) reacting a piperazinyllkylamine of formula



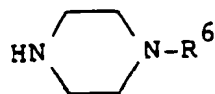
with a compound of formula



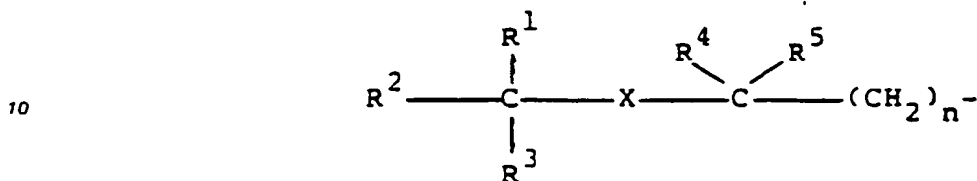
(where Hal is halogen) or

(h) alkylating a piperazine of formula

55

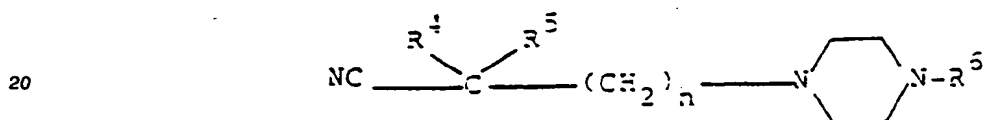


5 with an alkylating agent providing the group



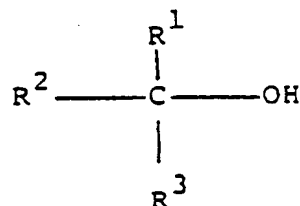
15 or

(i) reacting a nitrile of formula



with a tertiary alcohol of formula

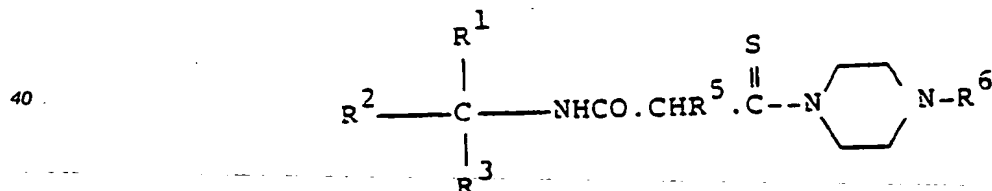
25



30

35 under acidic conditions or

(j) desulphurising a sulphur containing compound of formula



45

or

(k) converting a free base of formula (I) into a pharmaceutically acceptable salt thereof

or

(l) resolving a racemic compound of formula (I) to give an enantiomer.

50 2. A process as claimed in claim 1 in which, in the product,

R² and R³ are alkyl of 1 to 6 carbon atoms or taken together they are polymethylene of 2 to 6 carbon atoms or taken together with the carbon atom to which they are attached, R² and R³ complete a 5-norbornen-2-yl moiety;

55 R⁵ is hydrogen, alkyl of 1 to 6 carbon atoms, hydroxyalkyl of 1 to 3 carbon atoms, phenyl, benzyl, p-hydroxyphenyl, p-methoxyphenyl, o-methoxyphenyl, p-chlorophenyl or p-fluorophenyl; and

R⁶ is phenyl, 2-alkylphenyl in which the alkyl substituent has 1 to 6 carbon atoms, 2-alkoxyphenyl in which the alkoxy substituent has 1 to 6 carbon atoms, 2-halophenyl, 2-cyanophenyl, 2-nitrophenyl, 2-per-

halomethylphenyl, benzyl, 2-, 3- or 4-pyridinyl, 2-pyrimidinyl or 2-pyrazinyl;

or a pharmaceutically acceptable salt thereof, with the proviso that when X is -CON(R⁷)- and R⁷ is alkyl, R⁶ is other than 2-pyrimidinyl.

3. A process as claimed in Claim 2 in which R⁶ is 2-, 3- or 4-pyridinyl, 2-pyrimidinyl or 2-pyrazinyl, R¹, R² and R³ are methyl, R⁴ and R⁵ are hydrogen, X is -CO₂- or -NHCO₂, and n is 2.

4. A process as claimed in Claim 2 in which R⁶ is 2-methoxyphenyl, 2-chlorophenyl or 2-pyrimidinyl.

5. A process as claimed in as claimed in Claim 1 in which, in the product, R² and R³ are, independently, alkyl of 1 to 6 carbon atoms.

6. A process as claimed in of Claim 1 in which, in the product, R² and R³ are tetramethylene, pentamethylene or hexamethylene.

7. A process as claimed as claimed in any one of Claims 1, 5 or 6 in which, in the product, R⁴ is hydrogen and R⁵ is alkyl of 1 to 6 carbon atoms, phenyl or benzyl.

8. A process as claimed in of as claimed in any one of Claims 1, 5, 6 or 7 in which, in the product, R⁶ is 2-methoxyphenyl, 2-chlorophenyl or 2-pyrimidinyl.

9. A process as claimed in Claim 1 in which, in the product, R⁵ is alkyl of 4 to 8 carbon atoms, phenyl, benzyl, substituted phenyl or benzyl in which the substituents are halo, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, trifluoromethyl, nitro, cyano, carbalkoxy of 2 to 7 carbon atoms, carboxamido, alkylamino of 1 to 6 carbon atoms or dialkylamino of 2 to 12 carbon atoms.

10. A process as claimed in claim 9 in which, in the product, X is N(R⁷)CO or -OCO, where R⁷ is hydrogen or alkyl of 1 to 6 carbon atoms, n is 1 and R² and R³ are, independently, alkyl of 1 to 6 carbon atoms.

11. A process as claimed in claim 1 in which the product is N-(1,1-dimethylethyl)-N'-[4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl]urea, or a pharmaceutically acceptable salt thereof, or N-[4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl]-2, 2-dimethylpropanamide, or a pharmaceutically acceptable salt thereof, or

2,2-dimethylpropanoic acid 2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl ester, or a pharmaceutically acceptable salt thereof, or

2,2-dimethylpropanoic acid 3-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl ester, or a pharmaceutically acceptable salt thereof, or

2,2-dimethylpropanoic acid 3-[4-(2-chlorophenyl)-1-piperazinyl]ethyl ester, or a pharmaceutically acceptable salt thereof, or

2,2-dimethylpropanoic acid 3-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl ester, or a pharmaceutically acceptable salt thereof, or

(R)-N-[1-methyl-2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl trimethylacetamide, or a pharmaceutically acceptable salt thereof, or

N-2-(4-(2-methoxyphenyl)-1-piperazine)ethyl 2,2-dimethylpropanamide or a pharmaceutically acceptable salt thereof, or

N-(1,1-dimethylethyl)-4-(2-methoxyphenyl)-1-piperazine acetamide, or a pharmaceutically acceptable salt thereof, or

N-(1,1-dimethylethyl)-4-(2-pyrimidinyl)-1-piperazinepropanamide, or a pharmaceutically acceptable salt thereof, or

2,2-dimethylpropanoic acid 2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl ether, or a pharmaceutically acceptable salt thereof, or

tertiary-butyl 3-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylpropanoate, or a pharmaceutically acceptable salt thereof, or

N-tertiary-butyl 3-[4-(2-methoxyphenyl)piperazinyl]-2-phenylpropanamide, or a pharmaceutically acceptable salt thereof, or

N-tertiary-butyl 2-[[4-(2-methoxyphenyl)piperazinyl]methyl]-3-phenylpropanamide, or a pharmaceutically acceptable salt thereof, or

N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-1-methylcyclohexanecarboxamide, or a pharmaceutically acceptable salt thereof, or

4-(2-methoxyphenyl)-N-(1-methylcyclohexyl)-1-piperazinepropanamide, or a pharmaceutically acceptable salt thereof, or

4-(2-pyrimidinyl)-N-(1-methylcyclohexyl)-1-piperazinepropanamide, or a pharmaceutically acceptable salt thereof, or

N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(1-methylcyclohexyl)urea, or a pharmaceutically acceptable salt thereof, or

N-2-(4-(2-pyrimidinyl)-1-piperazinyl)ethyl-1-methylcyclohexylcarboxamide, or a pharmaceutically acceptable

salt thereof, or

(R)-N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]-1-methylethyl]-1-methylcyclohexane carboxamide, or a pharmaceutically acceptable salt thereof, or

(R)-1-methyl-N-[1-methyl-2-[4-(2-pyrimidinyl)]-1-piperazinyl]ethylcyclohexane carboxamide, or a pharmaceutically acceptable salt thereof, or

N-(1,1-dimethylethyl)-3-[4-(2-methoxyphenyl)-1-piperazinyl]-propanamide, or a pharmaceutically acceptable salt thereof, or

2,2-dimethylpropanoic acid 2-(4-(2-methoxyphenyl)piperazin-1-yl)-1-phenylethyl ester, or a pharmaceutically acceptable salt thereof, or

O-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)-N-(2-methyl-2-propyl)carbamate, or a pharmaceutically acceptable salt thereof, or

N-tert-butyl-2-methoxyphenyl-3-(4-(2-methoxyphenyl)-piperazin-1-yl)propanamide, or a pharmaceutically acceptable salt thereof, or

N-tert-butyl-3-[1-[4-(2-methoxy)phenyl]piperazinyl]-2-phenyl-propionhydrazide, or a pharmaceutically acceptable salt thereof, or

O-tert-butyl-3-[1-(4-(2-methoxy)phenyl)piperazinyl]-2-phenyl-propionhydroxamate, or a pharmaceutically acceptable salt thereof, or

(R*)-N-tertiary butyl-3-[4-(2-methoxy)phenyl]piperazin-1-yl]-2-phenylpropionamide, or a pharmaceutically acceptable salt thereof, or

(S*)-N-tertiary butyl-3-[4-(2-methoxy)phenyl]piperazin-1-yl]-2-phenylpropionamide, or a pharmaceutically acceptable salt thereof.

12. A process for preparing a pharmaceutical composition comprising bringing a compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof, into association with a pharmaceutically acceptable carrier.

13. A process as claimed in claim 12 wherein the active ingredient is prepared by the process claimed in any one of claims 1 to 11.

(19)



Europäisches Patentamt
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Office européen des brevets



(11) Publication number:

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(12)

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(51) Int. Cl.⁵: **C07D 295/08, C07D 295/12,
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C07D 239/42**

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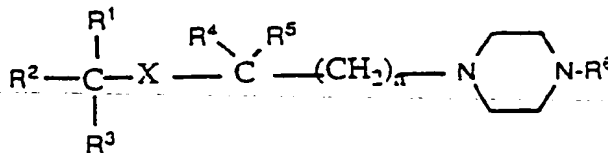
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(54) **Tertiary alkyl functionalized piperazine derivatives.**

(57) Compounds of the formula



in which R¹ is alkyl; R² and R³ are alkyl or taken together they are polymethylene, R² and R³ complete a 5-norbornen-2-yl moiety; X is -CO₂-, -OCO-, -OCO₂-, -N(R⁷)CO-, -NHNHCO-, -ON(R⁷)CO-, -CON(R⁷)-, -N(R⁷)CO₂-, -OCON(R⁷)- or -N(R⁷)CON(R⁸)-, wherein R⁷ and R⁸ are, independently, hydrogen, alkyl, phenyl, benzyl, substituted phenyl or substituted benzyl in which the substituents are halo, alkyl, alkoxy, cyano, nitro or perhalomethyl; R⁴ is hydrogen or alkyl; R⁵ is hydrogen, alkyl, hydroxyalkyl, phenyl, benzyl, substituted phenyl or substituted benzyl in which the substituents are hydroxy, halo, alkyl, alkoxy, trifluoromethyl, nitro, cyano, carbalkoxy, carboxamido, amino, alkylamino, or dialkylamino; R⁶ is phenyl, benzyl, 2-, 3-, or 4-pyridinyl, 2-pyrimidinyl or 2-pyrazinyl, any of which may be substituted by one or more hydroxy, halo, alkyl, alkoxy, trifluoromethyl, nitro, cyano, carbalkoxy, carboxamido, amino, alkylamino or dialkylamino; n is one of the integers 1, 2, 3, 4 or 5; or a pharmaceutically acceptable salt thereof, with the proviso that when X is -CON(R⁷)- and R⁷ is alkyl, R⁶ is other than 2-pyrimidinyl, are antidepressant and/or anxiolytic agents.

EP 0 395 313 A3



European
Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 30 4251

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 048 045 (DUPHAR INTERNATIONAL) * Claims * - - - -	1,2,5-7, 10,12-14	C 07 D 295/08 C 07 D 295/12 C 07 D 295/14
D,X	US-A-4 202 898 (DEPOORTERE) * Example 21; claims * - - - -	1,2,5,7,8, 10,12-14	A 61 K 31/495 C 07 D 239/42
A	EP-A-0 015 615 (DUPHUR INTERNATIONAL) * Whole document * - - - -	1-14	
A	GB-A-2 155 925 (BRISTOL-MYERS CO.) * Examples; claims * - - - -	1-14	
A	EP-A-0 238 905 (MERRELL DOW) * Example 2; claims * - - - -	1-14	
D,A	US-A-4 797 489 (ABOU-GHARBIA et al.) * Examples; claims * - - - - -	1-14	
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int. Cl.5) C 07 D 295/00 C 07 D 239/00
Place of search The Hague		Date of completion of search 20 February 91	Examiner HELPS I.M.
<div>CATEGORY OF CITED DOCUMENTS</div> <div>X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention</div> <div>E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons ----- &: member of the same patent family, corresponding document</div>			